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# Radical Amination with Trimethylstannylated Benzophenone Imine

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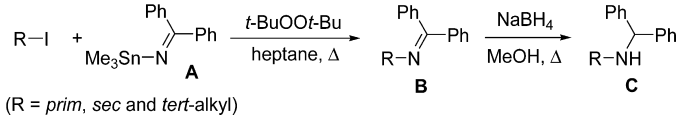
## ABSTRACT




(R = *prim*, *sec* and *tert*-alkyl)

**Intermolecular radical amination reactions of various primary, secondary, and tertiary alkyl radicals by using trimethylstannylated benzophenone imine A as a novel radical acceptor to provide imines of type B are described. These imines are readily reduced with $NaBH_4$ to the corresponding secondary amines C. The novel radical amination can be combined with typical radical cyclization reactions.**

Radical chemistry has found great attention during the last 20 years and is amply used in complex natural product synthesis.[1] Many functional groups are tolerated under radical conditions, and complex sequential processes can readily be performed by using this approach. As compared to radical C−C bond-forming reactions and C-radical reductions, radical carbon−heteroatom bond formation has been less intensively investigated. However, many natural products and most biologically interesting compounds (drugs) contain N-atoms. Therefore, development of new methods for C−N bond formation is important. By using radical chemistry, this bond connection can be performed by either addition of N-centered radicals to olefinic acceptors[2,3] or by addition of C-centered radicals to N-type acceptors.[4] The present paper focuses on the latter approach. Different reagents such as nitric oxide,[5] azo compounds,[6] diazirines,[7] diazonium salts,[8] and azides[9] have been successfully used as N-type acceptors for radical amination reactions. Moreover, appropriately substituted imines have been shown to be able to act as N-type radical acceptors.[10] However, to the best of our knowledge, all reports on imines as radical acceptors deal

(1) Renaud, P., Sibi, M. P., Eds. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, 2001.

(2) Reviews: Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337. Zard, S. Z. *Synlett* **1996**, 1148. Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (d) Stella, L. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 407.

(3) Kemper, J.; Studer, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4914. Walton, J. C.; Studer, A. *Acc. Chem. Res.* **2005**, *38*, 794. Guin, J.; Mück-Lichtenfeld, C.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2007**, *129*, 4498.

(4) Review: Ollivier, C.; Renaud, P. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds. Wiley-VCH: Weinheim, 2001; Vol. 2, p 93.

(5) Okamoto, T.; Oka, S. *J. Chem. Soc., Chem. Commun.* **1984**, 289. Patel, V. F.; Pattenden, G. *Tetrahedron Lett.* **1987**, *28*, 1451. Ghosez, A.; Göbel, T.; Giese, B. *Chem. Ber.* **1988**, *121*, 1807. Veit, A.; Giese, B. *Synlett* **1990**, 166.

(6) Huisgen, R.; Pohl, H. *Chem. Ber.* **1960**, *93*, 527. Shah, A.; George, M. V. *Tetrahedron* **1971**, *27*, 1291. Baigraie, B. D.; Cadogan, J. I. G.; Sharp, J. T. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1065. Beckwith, A. L. J.; Wang, S.; Warkentin, J. *J. Am. Chem. Soc.* **1987**, *109*, 5289. Wang, S. F.; Mathew, L.; Warkentin, J. *J. Am. Chem. Soc.* **1988**, *110*, 7235. (e) Kunka, C. P. A.; Warkentin, J. *Can. J. Chem.* **1990**, *68*, 575. Leardini, R.; Lucarini, M.; Nanni, A.; Nanni, D.; Pedulli, F. G.; Tundo, A.; Zanardi, G. *J. Org. Chem.* **1993**, *58*, 2419.

(7) Barton, D. H. R.; Jaszberenyi, J. Cs.; Theodorakis, E. A.; Reibenspies, J. H. *J. Am. Chem. Soc.* **1993**, *115*, 8050.

(8) Review: Heinrich, M. R. *Chem.—Eur. J.* **2009**, *15*, 820. Heinrich, M. R.; Blank, O.; Wölfel, S. *Org. Lett.* **2006**, *8*, 3323. Heinrich, M. R.; Blank, O.; Wetzel, A. *J. Org. Chem.* **2007**, *72*, 476. Blank, O.; Wetzel, A.; Ullrich, D.; Heinrich, M. R. *Eur. J. Org. Chem.* **2008**, 3179.

(9) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1994**, *116*, 5521. Kizil, M.; Murphy, J. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1409. Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2000**, *122*, 6496. Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2001**, *123*, 4717. Panchaud, P.; Chabaud, L.; Landais, Y.; Ollivier, C.; Renaud, P.; Zigmantas, S. *Chem.—Eur. J.* **2004**, *10*, 3606. Nyfeler, E.; Renaud, P. *Org. Lett.* **2008**, *10*, 985. Mantrand, N.; Renaud, P. *Tetrahedron* **2008**, *64*, 11860. Cren, S.; Schär, P.; Renaud, P.; Schenk, K. *J. Org. Chem.* **2009**, *74*, 2942.

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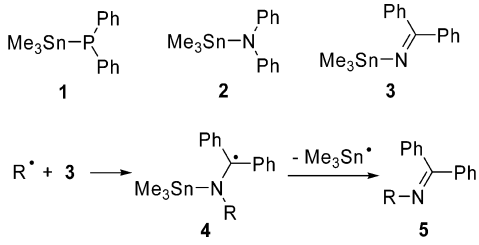
with cyclization reactions. Herein we present the first intermolecular radical aminations onto imines by using *N*-trimethylstannylated benzophenone imine **3** as a novel radical acceptor (Scheme 1).

**Scheme 1.** Radical Amination with **3**




Recently, we reported on radical phosphanylations with stannylated phosphine **1**.[11] C-Radical addition to the P-atom of **1** turned out to be very fast. The adduct radical then liberates the trimethyltin radical which is able to propagate the chain. This process corresponds to a formal homolytic substitution at phosphorus. Based on these results, we decided to test homolytic substitution at the trimethylstannylated amine **2**.[12] Unfortunately, all amination attempts with **2** by using various C-radicals under different conditions failed. We therefore decided to approach the intermolecular radical amination by an addition/elimination sequence with an imine as a radical acceptor. In order to get regioselective N-addition, phenyl groups were installed at the imine functionality (see **3**). Addition of a C-radical to **3** should generate adduct radical **4** which will then eliminate the chain propagating trimethyltin radical to provide the targeted imine **5**.

The known amination reagent **3** was readily prepared by reaction of benzonitrile with commercially available Ph-Li and subsequent treatment with $Me_3SnCl$ in $Et_2O$ (see the Supporting Information).[13] Imine **3**, which was purified by distillation, could be stored under argon in the refrigerator for months.

As a test reaction we studied amination of cyclohexyl iodide with **3** under different conditions (Table 1). All experiments were conducted in sealed tubes. With α,α′-azobisisobutyronitrile (AIBN) as an initiator, the reaction did not work (entries 1 and 2). With 1,1′-azobis(cyclohexane-1-carbonitrile) (V-40) as an alternative azo initiator product formation was not observed (entry 6). Pleasingly, with di-*tert*-butyl hypodinitrite[14] at 60 °C in benzene, imine **5** was obtained, clearly showing that our new approach for intermolecular radical amination is working. However, the product was isolated in a moderate 24% yield (entry 3). A similar result was achieved in *n*-heptane (entry 4) and initiation with $Et_3B/O_2$[15] afforded **5** in a lower yield (entry 5). Benzoyl and lauroyl peroxide turned out to be less efficient initiators for our radical amination (entries 7 and 8). Di-*tert*-butyl peroxide (DTBP) as initiator in benzene gave **5** in 15% yield (entry 9). We assumed that radical addition to benzene might occur as a side reaction that would lead to chain termination. Indeed, in *tert*-butylbenzene, which is less prone to undergo homolytic aromatic substitution, yield could be improved to 38% (entry 10). Along this line, yield was further improved in *n*-heptane under otherwise identical conditions (61%, entry 11).[16] The radical nature of the process was supported by running the amination in the absence of any initiator. As expected for a radical process, no product was identified by GC analysis under these conditions (entry 12). This experiment clearly showed that **5** was not formed via a $S_N2$-type process. Lowering the amount of **3** from 1.5 to 1.25 equiv led to a decrease in yield, whereas increasing reagent loading to 1.75 did not significantly change reaction outcome and with 2 equiv of **3** the best result was achieved (entries 13−15). Di-*tert*-butyl peroxide (0.25 equiv) turned out to be the ideal initiator loading since lowering the peroxide amount led to a decrease in yield (entries 16−18).[17]

We next studied the scope and limitations of the amination reaction applying the optimized conditions (di-*tert*-butyl peroxide (0.25 equiv) in *n*-heptane in a sealed tube at 140 °C oil bath temperature and 2 equiv of **3**). For some derivatives we observed partial decomposition of the product imines of type **5** during $SiO_2$ chromatography. In those cases, the crude imine was reduced with $NaBH_4$ in MeOH to give the corresponding bulky secondary amines of type **6**, which were readily isolated by

(10) Han, O.; Frey, P. A. *J. Am. Chem. Soc.* **1990**, *112*, 8982. Takanao, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Chem. Lett.* **1990**, 315. Tomaszewski, M. T.; Warkentin, J. *Tetrahedron Lett.* **1992**, *33*, 2123. Tomaszewski, M. T.; Warkentin, J. *J. Chem. Soc., Chem. Commun.* **1993**, *11*, 966. Takano, S.; Suzuki, M.; Ogasawara, K. *Heterocycles* **1994**, *37*, 149. Bowman, R. W.; Stephenson, P. T.; Terret, N. K.; Young, A. R. *Tetrahedron Lett.* **1994**, *35*, 6369. Bowman, R. W.; Stephenson, P. T.; Terret, N. K.; Young, A. R. *Tetrahedron* **1995**, *51*, 7959. Gioanola, M.; Leardini, R.; Nanni, D.; Pareschi, P.; Zanardi, G. *Tetrahedron* **1995**, *51*, 2039. McClure, C. K.; Kiessling, A. J.; Link, J. S. *Tetrahedron* **1998**, *54*, 7121. Ryu, I.; Matsu, K.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **1998**, *120*, 5838. Depature, M.; Diewok, J.; Grimaldi, J.; Hatem, J. *Eur. J. Org. Chem.* **2000**, 275. Johnston, J. N.; Plotkin, M. A.; Viswanathan, R.; Prabhakaran, E. N. *Org. Lett.* **2001**, *3*, 1009. Viswanathan, R.; Prabhakaran, E. N.; Plotkin, M. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 163. Tojino, M.; Otsuka, N.; Fukuyama, T.; Matsubara, H.; Ryu, I. *J. Am. Chem. Soc.* **2006**, *128*, 7712.

(11) Vaillard, S. E.; Mück-Lichtenfeld, C.; Grimme, S.; Studer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6533.

(12) For a formal homolytic substitution at N, see: Uenoyama, Y.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2007**, *9*, 935.

(13) Chan, L. H.; Rochow, E. G. *J. Organomet. Chem.* **1967**, *9*, 231.

(14) Mendelhall, G. D. *Tetrahedron Lett.* **1983**, *24*, 451.

(15) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Soc. Chem. Jpn.* **1989**, *62*, 143.

(16) As side products, protected amines derived from amination of heptane were identified. Alkoxyl radicals abstract H-atoms from *n*-heptane under the applied conditions. All possible regioisomeric *n*-heptane amination products were identified by GC analysis.

(17) Further increase of the di-*tert*-butyl concentration (>0.2 equiv) provided larger amounts of heptane amination side products.

(18) For conversion of imines to free amines, see: Sampson, P. B.; Honek, J. F. *Org. Lett.* **1999**, *1*, 1395. Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, Y.; Tayama, E.; Sakai, D.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 5073.

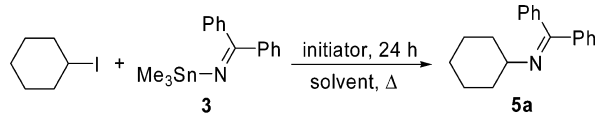
(19) Jereb, M.; Zupan, M.; Stavber, S. *Green. Chem.* **2005**, *7*, 100.

(20) Hackmann, C.; Schäfer, H. J. *Tetrahedron* **1993**, *49*, 4559.

(21) Review: Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813. See also: Studer, A. *Angew. Chem., Int. Ed.* **1998**, *31*, 462. Studer, A.; Steen, H. *Chem.—Eur. J.* **1999**, *5*, 759.

(22) CCDC 760806 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (int.) +44(1223)336-033, E-mail: deposit@ccdc.cam.ac.uk].

**Table 1.** Amination of Cyclohexyl Iodide with **3** under Different Conditions (0.5 M)




| entry | **3** (equiv) | solvent | initiator (equiv) | temp (°C) | yield[a] (%) |
|---|---|---|---|---|---|
| 1 | 1.5 | *n*-heptane | AIBN (0.25) | 140 | <2 |
| 2 | 1.5 | benzene | AIBN (0.25) | 115 | <2 |
| 3 | 1.5 | benzene | *t*-BuON=NO-*t*-Bu (0.25) | 60 | 24 |
| 4 | 1.5 | *n*-heptane | *t*-BuON=NO-*t*-Bu (0.25) | 60 | 22 |
| 5 | 1.5 | benzene | $Et_3B/O_2$ (0.25) | 60 | 14 |
| 6 | 1.5 | *n*-heptane | V-40 (0.25) | 80 | <2 |
| 7 | 1.5[b] | *n*-heptane | lauroyl peroxide (0.25) | 140 | 19 |
| 8 | 1.5[b] | *n*-heptane | benzoyl peroxide (0.25) | 140 | 8 |
| 9 | 1.5 | benzene | *t*-BuOO-*t*-Bu (0.25) | 115 | 15 |
| 10 | 1.5 | *t*-Bu-benzene | *t*-BuOO-*t*-Bu (0.25) | 140 | 38 |
| 11 | 1.5 | *n*-heptane | *t*-BuOO-*t*-Bu (0.25) | 140 | 61 |
| 12 | 1.5 | *n*-heptane | | 140 | <2 |
| 13 | 1.25[c] | *n*-heptane | *t*-BuOO-*t*-Bu (0.25) | 140 | 37 |
| 14 | 1.75[c]c | *n*-heptane | *t*-BuOO-*t*-Bu (0.25) | 140 | 54 |
| 15 | 2.0 | *n*-heptane | *t*-BuOO-*t*-Bu (0.25) | 140 | 62 |
| 16 | 1.5 | *n*-heptane | *t*-BuOO-*t*-Bu (0.10) | 140 | 9 |
| 17 | 1.5 | *n*-heptane | *t*-BuOO-*t*-Bu (0.15) | 140 | 37 |
| 18 | 1.5 | *n*-heptane | *t*-BuOO-*t*-Bu (0.20) | 140 | 60 |

[a] Isolated yield after $SiO_2$ chromatography. [b] Conducted at 0.2 M concentration. [c] Conducted at 0.7 M concentration.

chromatography.[18] All aminations were conducted with the corresponding alkyl iodides since reactions did not work well starting with bromides.

Amination of cyclohexyl iodide with subsequent reduction provided amine **6a** in 84% yield (Figure 1). This result showed that during purification of imine **5a** some product was decomposed (compare Table 1, entry 15). An even better result was obtained for amination of pentyl iodide to give **6b** (87% yield). Functionalized primary alkyl radicals also underwent amination as shown for the preparation of **5f** and **6d**. Pleasingly, tertiary-alkyl radicals reacted efficiently with **3** (see **6c**). Amination of α-silyloxy or α-alkoxyalkyl radicals provided the corresponding protected α,β-amino alcohols **6e** and **6g**. Due to the high temperatures used it was not surprising that amination occurred with low diastereoselectivity (*trans*/*cis* = 1.2:1, see **6e**). Protected amino sugars such as **5h** can be obtained via our approach starting with readily available iodo glycosides.[19] Unfortunately, aryl and vinyl radicals could not be aminated with reagent **3** under the tested conditions.

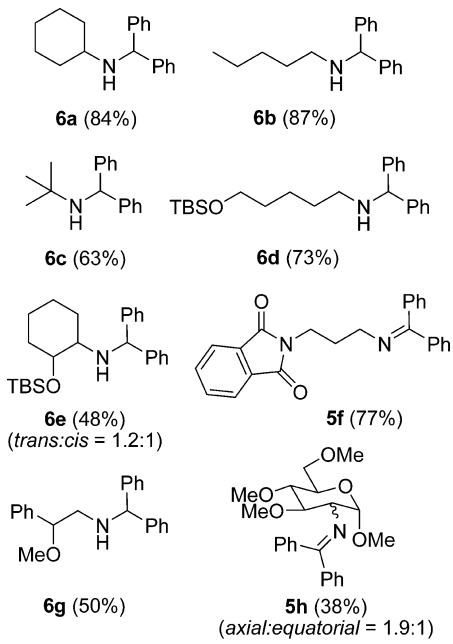
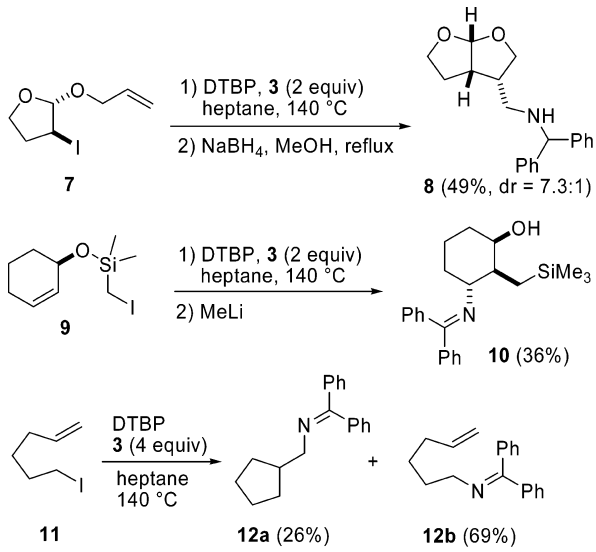



**Figure 1.** Amination products.

Finally, we looked at cascade reactions comprising a typical radical cyclization reaction followed by amination. To this end, iodide **7** was reacted with imine **3** under our optimized amination conditions. The crude product was reduced with $NaBH_4$, and bicycle **8** was isolated as a 7.3:1 mixture of diastereoisomers (checked by $^1H$ NMR spectroscopy) in 49% yield. The relative configuration of the major isomer depicted in Scheme 2 was assigned by comparison with product assignments of similar radical cyclization reactions.[20] Iodinated silyl ether **9** underwent radical 5-*exo*-cyclization with subsequent amination. The intermediately formed cyclic silyl ether was then reacted with MeLi[21] to give imine **10** as a single isomer. The relative configuration of **10** was unambiguously assigned by X-ray analysis (Figure 2).[22]

The 5-*exo*-radical cyclization reaction of the 5-hexenyl radical has been intensively used as a radical clock for

**Scheme 2.** Radical Cyclization/Amination with **3**




determination of the rate constant for reaction of a primary alkyl radical with a given radical trapping reagent.[23] To get an idea about the efficiency of our amination process, we reacted iodide **11** under radical conditions with either 3 or 4 equiv of imine **3** to give a mixture of cyclized **12a** and noncyclized imine **12b**. The two experiments were repeated two times (each) and the rate constant was estimated on the basis of averaged **12a/12b** ratios of these six experiments. By using the experimentally determined rate constant for that particular 5-*exo* cyclization at 140 °C ($6.15 \times 10^6$ $s^{-1}$),[24] we calculated the rate constant for trapping of a primary alkyl radical with imine **3** to lie in the order of $5 \times 10^6$ $M^{-1}$ $s^{-1}$ at 140 °C.

(23) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.
(24) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739.

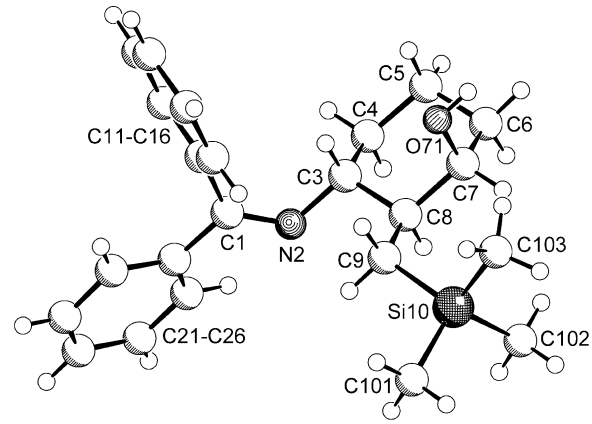



**Figure 2.** Molecular structure of **10**.

In summary, we introduced stannylated imine **3** as a novel reagent for intermolecular radical aminations. Aminations can be conducted as cascade processes comprising typical radical cyclizations with subsequent C−N bond formations. Product imines are protected amines since the imine moiety installed by the radical reaction can be regarded as the N-protecting group. Moreover, imines can be reduced to the corresponding secondary amines.

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**Supporting Information Available:** Experimental details, characterization data for the products, and the X-ray structure of **10** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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