

Radical Amination with Trimethylstannylated Benzophenone Imine

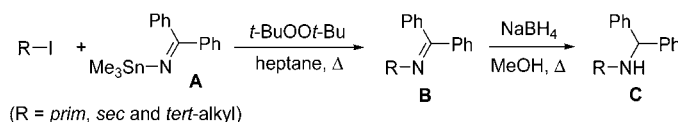
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ABSTRACT



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 azides⁹ 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

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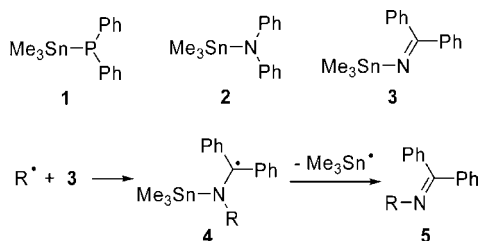
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with cyclization reactions. Herein we present the first intermolecular radical aminations onto imines by using *N*-trimethylstannylated benzophenone imine **3** as a novel radical acceptor (Scheme 1).

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 hypodinitrite¹⁴ 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 $\text{Et}_3\text{B}/\text{O}_2$ 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 $\text{S}_\text{N}2$ -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

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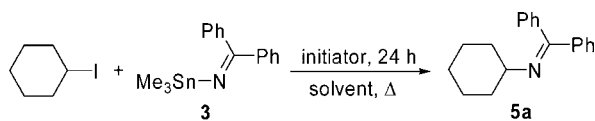
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Table 1. Amination of Cyclohexyl Iodide with **3** under Different Conditions (0.5 M)

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

^a Isolated yield after SiO₂ chromatography. ^b Conducted at 0.2 M concentration. ^c Conducted at 0.7 M concentration.

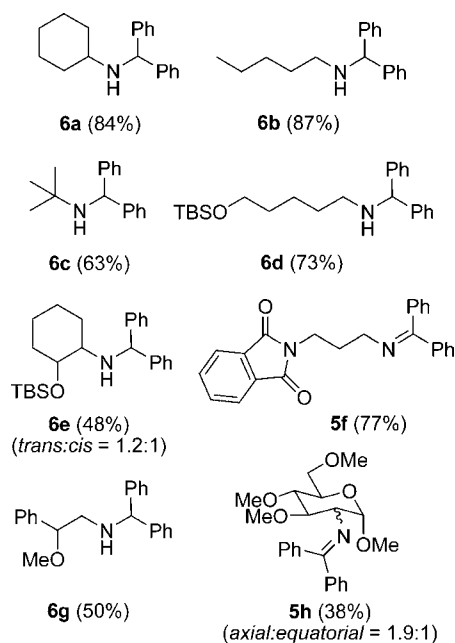
chromatography.¹⁸ All aminations were conducted with the corresponding alkyl iodides since reactions did not work well starting with bromides.

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

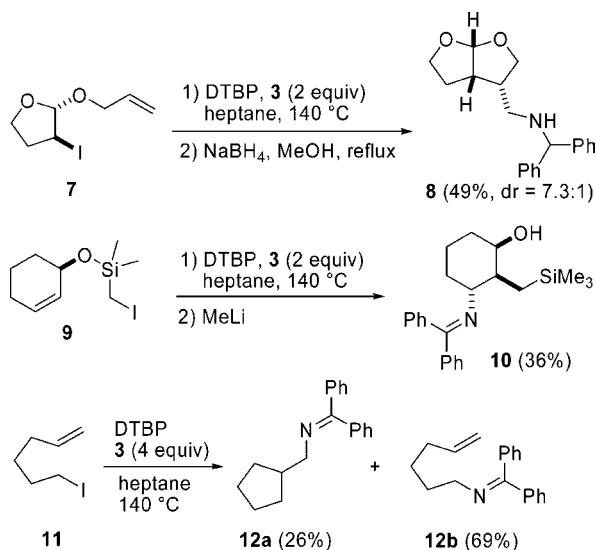
was decomposed (compare Table 1, entry 15). An even better result was obtained for amination of pentyl iodide to give **6b** (87% yield). Functionalized primary alkyl radicals also underwent amination as shown for the preparation of **5f** and **6d**. Pleasingly, tertiary-alkyl radicals reacted efficiently 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.

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 NaBH₄, 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 MeLi²¹ 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

**Figure 1.** Amination products.

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 ($6.15 \times 10^6 \text{ s}^{-1}$),²⁴ we calculated the rate constant for trapping of a primary alkyl radical with imine **3** to lie in the order of $5 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at 140 °C.

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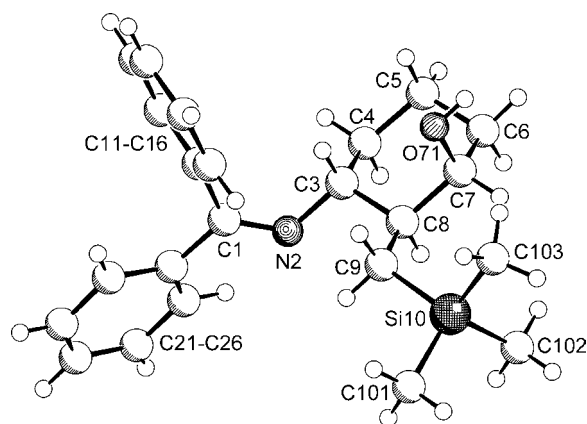


Figure 2. Molecular structure of **10**.

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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