New Methods towards the synthesis of beta-amino acids

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Chapter 5

Studies towards the Curtius rearrangement of thioesters for the synthesis of β-amino acids

The goal of this project was to perform a Curtius rearrangement of thioesters to synthesize the corresponding amines without prior hydrolysis. In combination with the catalytic asymmetric conjugate addition of Grignard reagents to fumarate derivatives (see chapter 6), this approach would represent a two-step procedure towards enantiomerically enriched β2- and β3-amino acids. Unfortunately, we failed so far to develop a successful procedure for the Curtius rearrangement of thioesters.
Chapter 5

5.1 Introduction

5.1.1 Curtius rearrangement

The Curtius rearrangement is an important synthetic method for the preparation of amines from carboxylic acids.\(^1\) It has been included in the preparation of many natural products and has also been used to synthesize \(\beta\)-amino acids (see chapter 1). In the general process, an acyl azide is converted by heating into the corresponding isocyanate. During the thermolysis, \(N_2\) is eliminated and at the same time a [1,2]-shift of the substituent next to the carbonyl group takes place with retention of configuration (scheme 5.01).\(^2\) The isocyanates \textit{5.02} can be transformed into (protected) amines by hydrolysis and alcoholysis after workup or \textit{in situ} by performing the rearrangement in alcoholic solvents.

\[
\begin{align*}
\text{R}^+\text{N}=\text{N}=\text{N} & \xrightarrow{\Delta} \text{R}^\text{N}=\text{N}=\text{O} \\
\text{R}^\text{N}=\text{N}=\text{O} & \xrightarrow{\text{H}_2\text{O}^+} \text{R}^\text{N}=\text{O} \\
\text{R}^\text{N}=\text{O} & \xrightarrow{\text{R}^\text{OH}} \text{R}^\text{N}^\text{Boc}\text{O} \\
\end{align*}
\]

\textit{Scheme 5.01. General mechanism for the Curtius rearrangement.}

In general, acyl azides are prepared from activated carboxylic acid derivatives such as acyl chlorides\(^3\) or anhydrides\(^4,5\). Direct conversion of carboxylic acids has been reported using diphenylphosphoryl azide (dppa) in a one pot procedure.\(^6\) This method has the advantage that the generally explosive acyl azides do not have to be isolated. First, a mixed anhydride of carboxylic acid/phosphoric acid \textit{5.07} is formed and azide is eliminated. Anhydride \textit{5.07} acylates the azide anion to form acyl azide \textit{5.01} which then rearranges to the corresponding isocyanate \textit{5.02} (scheme 5.02). With \textit{tert}-butanol as solvent, the isocyanate \textit{5.02} was solvolized to the \(N\)-Boc-protected amine \textit{5.08}. 

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Aldehydes can also be converted directly to acyl azides using oxidative conditions or radical azidation (scheme 5.03). Using Dess-Martin periodinane or tert-butyl hypochlorite, aromatic and aliphatic aldehydes were transformed to the corresponding acyl azides in high yield (scheme 5.03a). The radical azidation of aromatic and aliphatic aldehydes with iodine azide IN₃ gave upon heating the corresponding isocyanates. With more than one equivalent of IN₃ (formed from two equivalents of ICl and three equivalents of NaN₃) the carbamoyl azide was formed which could be hydrolyzed to the corresponding amine using a base (scheme 5.03b).

Up to date, there has been no procedure reported for the direct conversion of thioesters or oxoesters to acyl azides and subsequent Curtius rearrangement.

5.1.2 Conversion of thioesters to carboxylic acids and esters

The activation of thioesters using thiophilic metal ions such as Cu(II), Ag(I), Hg(II), and Zn(II) has been described for transesterification reactions. Furthermore, hydrolysis rates for thioesters are increased upon oxidation of the thioester residue with peroxymonsulfate. The final products are the corresponding carboxylic acid and sulfonic acid (scheme 5.04). The authors propose that initially the thiol is oxidized to the
acyl sulfoxide which then breaks down to give the carboxylic acid and a sulfenic acid which will be rapidly oxidized to the corresponding sulfonic acid 5.14.

\[
\begin{align*}
\text{Scheme 5.04. Accelerated hydrolysis of thioesters by oxidation.}
\end{align*}
\]

Ti(O-i-Pr)₄ was used to activate ethylthio ester 5.15 for the transesterification with ethanol (scheme 5.05).¹⁰ The equilibrium was shifted to the oxoester due to the volatility of the released ethanethiol.

\[
\begin{align*}
\text{Scheme 5.05. Transesterification mediated by TiIV.}
\end{align*}
\]

Several examples have been reported in which Cu I- and Cu II-salts were employed to activate thioesters (scheme 5.06).¹¹ The transesterification of 2-pyridyl thioates 5.17 to the corresponding esters 5.18 was mediated by CuBr₂ (scheme 5.06a).¹¹a Several aliphatic and aromatic esters were synthesized with this method. For the intramolecular synthesis of \(\beta\)-lactams, the amino-thioester 5.19 was treated with CuOTf and CaCO₃ to give the amides in good yield (scheme 5.06b).¹¹b The alcohol group of compound 5.21, obtained from a hetero Diels-Alder reaction followed by a subsequent conjugate addition and reduction of the carbonyl group, was cyclized in the presence of Cu(OTf)₂ (scheme 5.06c).¹¹c The product 5.22 was further converted into (+)-9-deoxygoniopyrone, which shows cytotoxic activity against tumor cells.
Chapter 5: Studies towards the Curtius rearrangement of thioesters

Mercury(II)-salts have been used to facilitate the transesterification of thioesters (Scheme 5.07).\textsuperscript{12} For the synthesis of galbonolide B, the macrocycle 5.24 was formed through bond formation between the alcohol and the thioester moiety assisted by Hg(OAc)\textsubscript{2} (scheme 5.07a).\textsuperscript{12a} Compound 5.25 was formed by 1,4-addition to 4-OTBS-2-cyclohexenone followed by quenching with NH\textsubscript{4}Cl at room temperature. The thioacetal was cleaved mediated by HgO in methanol to give 5.26 (scheme 5.07b).\textsuperscript{12b} The 4[(bismethylthio)ethylidene] functionality present in 5.27 was transformed to the propanoate 5.28 upon methanolysis in the presence of BF\textsubscript{3} and HgCl\textsubscript{2} (scheme 5.07c).\textsuperscript{12c}
Silver triflate was also used to facilitate macrolactonizations or transesterification of thioesters and alcohols (Scheme 5.08). Sodeoka and coworkers used AgOTf to mediate macrolactonization of 5.29 to form 5.30 (scheme 5.08a). Transesterification of 5.31 was facilitated with AgOTf to give ester 5.32 in good yield (scheme 5.08b). The products are intermediates in the synthesis of a tetronic acid library as inhibitors for protein phosphatases. During the synthesis of RK-682, Sodeoka and coworkers transesterified thioester 5.33 with alcohol 5.34 to give ester 5.35 (scheme 5.08c).
Chapter 5: Studies towards the Curtius rearrangement of thioesters

The objective of the project described here was to find conditions for the Curtius rearrangement of thioesters and to integrate it in a synthetic route to β-amino acids described in chapter 6 (scheme 5.09).

5.2 Curtius rearrangement starting from thioesters

Thioester 5.41 was synthesized from ethanethiol and octanoic acid 5.40 by activation with dicyclohexylcarbodiimide (DCC) and catalytic amounts of (dimethylamino)pyridine (DMAP) in good yield (scheme 5.09). This thioester with a long alkyl chain was chosen for screening purposes. Azides are generally accepted to be safe for isolation on multigram scale if the sum of the oxygen and carbon atoms is greater than three times the number of (azide) nitrogens.14
First, only NaN₃ was used as a nucleophile in various solvents but no reaction was observed (table 5.1, entry 1-6). Phase transfer reagent tetra-n-butylammonium bromide was used to improve the solubility of the nucleophile, but no acyl azide was formed either (table 5.1, entry 7, 9, 11). DMAP was used to activate and transform the thioester, and different solvents were screened, as well as the combination of DMAP and the phase transfer reagent (table 5.1, entry 8-11). However, no conversion was observed. Activating the thioester with the Lewis acid BF₃·OEt₂ did not yield the acyl azide either (table 5.1, entry 12). Using Meerwein salt (trimethylxonium tetrafluoroborate) to methylate the thioester or to methylate the released ethanethiol was also not successful to synthesize the acyl azide (table 5.1, entry 13). A procedure based on the addition of 18-crown-6 to encapsulate the sodium ion, and therefore produce a ‘naked’ azide ion, did not show any conversion of the thioester (table 5.1, entry 14). With DBU as basic additive in acetonitrile or toluene, no reaction of the thioester was observed (table 5.1, entry 15-16).
Table 5.1. Screening of additives and solvents for the acyl azide formation from thioesters.

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^a Monitored by GC-MS.

Next, various metal salts were screened, some of them thiophilic and some strong Lewis acids, sometimes in combination with the Lewis acid BF₃OEt₂ to activate the carbonyl oxygen. Thiophilic metals, Hg²⁺, Cd²⁺, Pb²⁺, Ni²⁺, Ag⁺, As³⁺, Sb³⁺, Co³⁺, Bi³⁺, Cu²⁺, Zn²⁺, Fe³⁺, Mn³⁺, Pd²⁺, form strong complexes with thiols or sulfides. The precipitation of metal sulfides is used in analytical chemistry for the qualitative separation of cations. However, some of these metal salts are highly toxic, such as those based on Hg²⁺, Pb²⁺, Cd²⁺, As³⁺, Ni²⁺, and their use in organic synthesis of pharmaceuticals is not recommended.
### Table 5.2. Screening of metal salt additives for the Curtius rearrangement starting from thioesters.

![Structural formula](image)

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Chapter 5: Studies towards the Curtius rearrangement of thioesters

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<td>toluene</td>
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<tr>
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<td>1.2</td>
<td>1.5</td>
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<tr>
<td>29</td>
<td>Ti(Oi-Pr)₄</td>
<td>1.5</td>
<td>1.8</td>
<td>MeCN</td>
<td>50</td>
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<tr>
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<td>Ti(Oi-Pr)₄</td>
<td>1.5</td>
<td>1.8</td>
<td>1,2-dichloro-ethane</td>
<td>50</td>
<td>90</td>
<td>octanoic acid</td>
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</table>

31  FeCl₃  1.5  1.5  toluene  100  100 octanoic acid; mixture of products

32  FeCl₃  1.2  1.5  toluene  110  100 octanoic acid; mixture of products

33  FeCl₃  2.0  1.5  toluene  110  100 mixture of products

34  FeCl₃  1.3  1.8  MeCN  90  100 mixture of products

35  FeCl₃  1.3  1.8  1,2-dichloro-ethane  90  100 mixture of products

36  FeCl₃  1.3  1.8  DMF  90  100 mixture of products
Catalytic amounts of Zn(II)-triflate in combination with phase transfer reagent tetra-n-butylammonium bromide did not yield a reaction of thioester 5.41 (table 5.2, entry 1). A large excess of HgCl₂ (10 eq.) and NaN₃ (22 eq.) in benzene as solvent gave the desired isocyanate in ~20% yield (table 5.2, entry 2). Attempts to reduce the amount of mercury salt and sodium azide to 2 and 4 equivalents, respectively, or replacing the solvent benzene with toluene, did not lead to conversion (table 5.2, entry 3-4). HgCl₂ alone (2-6 eq.) showed conversion of the thioester but many products were formed according to GC-MS and ¹H NMR of whom none was the desired acyl azide or isocyanate (table 5.2, entry 5-6). Addition of AgOTf resulted in full conversion of the thioester but after treatment with tert-butanol, no Boc-protected amine was formed, nor could the free amine or the isocyanate be seen (table 5.2, entry 7). With AgOAc, no conversion was observed (table 5.2, entry 8). Copper(II)-triflate as additive showed only very low conversion of the thioester (<5%) after a reaction time of 3 days (table 5.2, entry 9). Copper(I)-bromide did not lead to the formation of products neither did Cu(I)-thienylcarboxylate (table 5.2, entry 10-11) Neither Raney-Nickel nor nickel(II)-chloride showed conversion of the thioester (table 5.2, entry 12-13). Cadmium(II)-chloride and tin(II)-chloride as additives showed mainly starting material after three days (table 5.2, entry 14-15). Adding the strong Lewis acid SbCl₅ to the reaction mixture lead to an immediate reaction that was indicated by a change of colour and increase of the temperature of the mixture. Performing the reaction in toluene, the crude ¹H NMR and GC-MS showed that the solvent had reacted and that the thioester was hydrolyzed (table 5.2, entry 16). In CH₂Cl₂ and Et₂O, only the thioester was isolated after column chromatography, although GC-MS showed the formation of several unidentified products (table 5.2, entry 17-18). InCl₃ as additive gave no conversion of thioester 5.41 as identified by ¹H NMR (table 5.2, entry 19). Studying SbCl₃ as additive, almost no conversion of the thioester was observed within a reaction time of 3 days (table 5.2, entry 20). BiBr₃ and Yb(OTf)₃ gave only conversion to octanoic acid (table 5.2, entry...
Palladium(II)-chloride added to the reaction mixture did not lead to conversion of the thioester neither did palladium(0)-species, in combination with PPh₃ and/or CuTC (table 5.2, entry 23-26). By adding Cs₂CO₃ as additive, the thioester did not show conversion (table 5.2, entry 27-28). Ti(Oi-Pr)₄ as Lewis acid in acetonitrile as solvent did not yield the isocyanate or the acyl azide, but in 1,2-dichloroethane the thioester showed conversion. The results were irresponsive, however, and only octanoic acid could be isolated (table 5.2, entry 29-30). Iron(III)-salts showed conversion of the thioester, but no conclusion could be drawn from the GC-MS data. Upon column chromatography, octanoic acid was isolated, even in a reaction under anhydrous conditions. This could indicate that a hydrolysis step occurred during workup. Using FeCl₃ hexahydrate, octanoic acid was formed along with other unidentified products (table 5.2, entry 31). Anhydrous FeCl₃ gave full conversion of the thioester, however, many products were formed, among them octanoic acid (table 5.2, entry 32). The same results were obtained when higher loadings of FeCl₃ were tested and acetonitrile, DMF, or 1,2-dichloroethane were used as solvents (table 5.2, entry 33-36). Adding aqueous NaOH in order to hydrolyze the isocyanate or carbamoyl azide did not give n-heptyl amine, indicating that neither an acyl azide nor an isocyanate was formed, e.g. a Curtius rearrangement had not taken place (table 5.2, entry 37-38). Additionally, BF₃ OEt₂ and FeCl₃ were combined, which led to very complex ¹H NMR and GC-MS spectra (table 5.2, entry 39). Iron(II)-salts showed no conversion of the thioester (table 5.2, entry 40).

The isocyanate obtained from thioester 5.41 with HgCl₂ and BF₃ OEt₂ as additives (table 5.2, entry 2) was heated at reflux in tert-butanol and toluene. After purification by column chromatography only 17% of N-Boc-n-heptylamine 5.44 was obtained (scheme 5.10). The reaction conditions were not further optimized because the isocyanate was only obtained when 10 eq. of highly toxic HgCl₂ in benzene as solvent were used. The reaction mixture is so toxic that this method can not be regarded as useful.

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5.43  \text{NCO} \xrightarrow{\text{t-BuOH, toluene}} 5.44 \text{NH}
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Scheme 5.10. Conversion of potential isocyanates.

Tetra-n-butylammonium azide was synthesized from sodium azide and tetra-n-butylammonium hydroxide (scheme 5.11). It is soluble in organic solvents and was studied for the conversion of thioester 5.41 to acyl azide 5.42. Using HgCl₂ or FeCl₃ as additives, no conversion of the thioester was observed.
Sulfinyl- or sulfonyl groups are more electrophilic than regular thioesters; therefore, oxidizing reagents were investigated for the conversion of thioesters to acyl azides (scheme 5.12). Addition of MCPBA did not give the desired oxidation products of the thioester but GC-MS and $^1$H NMR spectroscopy showed that octanoic acid 5.40 and mixed anhydride 5.47 were formed (scheme 5.13). The second product could result from an attack of residual $m$-chlorobenzoic acid. This means that the thioester might indeed be oxidized and that the intermediate oxidation product is very reactive. However, no nucleophilic oxidizing reagent nor aqueous conditions can be used because the oxidized thioester is sensitive to nucleophilic displacement.

Using Oxone (2 KHSO$_5$, KHSO$_4$, K$_2$SO$_4$) in methanol to oxidize the thioester, only methanolysis to methyl ester 5.48 was observed (scheme 5.14). However, in other organic solvents Oxone was not soluble.

Tetra-$n$-butylammonium Oxone was prepared via a procedure reported by Trost and coworkers to use this more soluble reagent instead of Oxone to oxidize the thioester.
The oxidation of sulfides to sulfones was reported with this reagent. Tetra-\(n\)-butylammonium Oxone is readily soluble in anhydrous organic solvents and was investigated instead of NaN\(_3\) in the oxidation of thioester 5.41 due to the fact that NaN\(_3\) is insoluble in organic solvents. Tetra-\(n\)-butylammonium hydroxide and Oxone gave the pure tetra-\(n\)-butylammonium Oxone in moderate yield.

\[
\text{Oxone} = \text{KHSO}_5, 0.5 \text{KHSO}_4, 0.5 \text{K}_2\text{SO}_4
\]

Scheme 5.15. Synthesis of tetra-\(n\)-butylammonium oxone.

This oxidant was used in the oxidation of thioester 5.41 (scheme 5.16). No conversion was observed in CH\(_2\)Cl\(_2\) as solvent. Also, when triethylamine as base was added, no reaction of the thioester took place.

\[
\text{Scheme 5.16. Oxidation of the thioester with Oxone and tetra-\(n\)-butylammonium Oxone.}
\]

In summary, we did not succeed in finding a suitable method to synthesize acyl azides or the rearranged isocyanates in good yield directly from thioesters. Metal salts as additives or oxidation of the thioester to activate it for azide substitution did not give the corresponding acyl azide or isocyanate. In some cases the hydrolyzed product, octanoic acid, was formed.

### 5.3 Conclusion

No procedure to successfully transform thioesters to acyl azides or isocyanates was found during this research. Many metal salt were investigated as additives. Moreover, activating reagents such as DMAP were studied. Only with ten equivalents of HgCl\(_2\) followed by subsequent hydrolysis of the isocyanate, the corresponding N-Boc protected amine was isolated in low yield. Decreasing the amount of mercury salts or changing the solvent to the less toxic toluene did not show sufficient conversion. This conditions were not further optimized because of the high toxicity of mercury and benzene. Investigations to use tetra-\(n\)-butylammonium azide, which is better soluble in organic solvents compared to sodium azide, did not lead to successful conversion of the thioester either. Oxidation of the thioester to a sulfinyl or sulfone moiety in order to increase the electrophilicity gave only nucleophilic displacement of the thioester with the solvent or oxidizing reagent. In general, thioesters are regarded as more reactive compared to their oxoester analogues. However, a substitution of the thioester with azide could not be
achieved. That could either result from thermodynamic properties, i.e. the equilibrium of the thioester cleavage, or have a kinetic origin due to a lack of reactivity. If the equilibrium of this substitution is on the side of the thioester, the formation of an acyl azide should be disfavored. However, attempts to trap the thiolytes for example with methylating reagents or by forming complexes with thiophilic metals to influence the equilibrium failed. Heating should start the Curtius rearrangement so that the acyl azide would be consumed to the isocyanate. That should also influence the equilibrium of an acyl azide formation from a thioester and drive it to the side of the acyl azide. Moreover, in those cases many side products were formed. Another reason for a failure of this reaction could be kinetic factors. The activation Gibbs energy of the transformation of the thioester to the acyl azide could be too high to overcome, for example compared to hydrolysis. In conclusion, we did not succeed to develop a direct route from thioesters to isocyanates. The thioester has to be hydrolyzed first to the corresponding carboxylic acid which then can undergo a Curtius rearrangement to give the respective amines.

5.4 Experimental

All reactions with NaN₃ were performed on small scale (0.25-0.50 mmol of the reagent) and with a safety screen in front of the reaction setup.

General methods. see chapter 2.

General procedure for the Curtius rearrangement. Thioester 5.41 (95 mg, 0.50 mmol, 1.0 eq.) was placed into a flask, and solvents (2-5 mL) and additives were added as indicated (see table 5.1 and 5.2), and the reaction mixture was stirred at the indicated temperature for up to 48h. Conversion and product formation was monitored by GC-MS.

Octanoic acid S-ethyl ester 5.41. N,N-Dicyclohexylcarbodiimide (13.0 g, 63.0 mmol, 1.27 eq.) was added to octanoic acid 7.90 mL, 49.8 mmol, 1.00 eq.), ethanethiol (11.1 mL, 150 mmol, 3.01 eq.) and 4-N,N-dimethylaminopyridine (0.44 g, 6.63 mmol, 7.30 mol%) in anhydrous CH₂Cl₂ (50 mL) at 0°C. The reaction mixture was stirred for 4h at room temperature, and filtered. The solvent was removed in vacuum, and CH₂Cl₂ (50 mL) was added. The organic layer was washed withaq. 0.5N aq. NaOH (30 mL) andaq. sat. NaHCO₃ (30 mL), dried over MgSO₄ and concentrated in vacuum. The crude product was purified by flash column chromatography (n-pentane/Et₂O 99/1) on silica gel to yield a colourless oil (7.97 g, 37.5 mmol, 75%).¹⁰¹H NMR (400 MHz, CDCl₃): δ=0.84 (t, 3J=6.8 Hz, 3H; CH₃), 1.17-1.31 (m, 11H; CH₂), 1.62 (t, 3J=6.6 Hz, 2H; CH₂), 2.50 (t, 3J=7.4 Hz, 2H; CH₂), 2.83 (q, 3J=7.5 Hz, 3H; CH₂).¹³C NMR (100 MHz, CDCl₃): δ=14.3 (CH₃), 15.0 (CH₃), 22.8 (CH₂), 23.4 (CH₂), 25.9 (CH₂), 29.1 (CH₂), 31.8 (CH₂), 44.3 (CH₂), 199.9 (CO). Spectral were data according to the literature.¹¹
Synthesis of tetra-\(n\)-butylammonium azide.\textsuperscript{18} A 40\% solution of tetra-\(n\)-butylammonium hydroxide (67.0 mL, 100 mmol) and sodium azide (13.0 g, 200 mmol, 2.00 eq.) were stirred in H\(_2\)O (30 mL) for 5 min. Then, CH\(_2\)Cl\(_2\) (150 mL) was added and the aqueous layer extracted three times with CH\(_2\)Cl\(_2\) (3 x 25 mL). After drying over MgSO\(_4\), the solvent was evaporated in vacuum and the remaining solid dried in vacuum (27.0 g, 95.0 mmol, 95\%). Data were according to the literature.\textsuperscript{18}

Synthesis of tetra-\(n\)-butylammonium Oxone (Bu\(_4\)N\(_5\) (HSO\(_5\))\(_2\)).\textsuperscript{19} Tetra-\(n\)-butylammonium hydrogen sulfate (30 g, 88 mmol, 2.5 eq.) was added to Oxone (11 g, 35 mmol) in H\(_2\)O (45 mL). The mixture was stirred for 3 h at room temperature. The aqueous layer was extracted three times with CH\(_2\)Cl\(_2\) (3 x 50 mL), dried over MgSO\(_4\) and concentrated in vacuum. The residual solid was dried in vacuum to give the pure product (27 g, 17.0 mmol, 48\%). Data were according to the literature.\textsuperscript{19}

**Heptyl-carbamic acid tert-butyl ester 5.44.** The crude isocyanate (max. 0.5 mmol) was dissolved in toluene (5 mL) and tert-butanol (0.18 g, 2.4 mmol) was added. After reflux overnight, the reaction mixture was cooled to room temperature, and H\(_2\)O and EtOAc were added. The organic layer was washed with aq. 1 N HCl, aq. sat. NaHCO\(_3\) and brine, dried over MgSO\(_4\) and concentrated in vacuum. Column chromatography (n-pentane) gave the pure product (0.02 g, 0.08 mmol, 17\%).\textsuperscript{22} \(\delta\)\textsuperscript{1}H NMR (400 MHz, CDCl\(_3\)): 0.88 (t, 3 \(J\) = 6.8 Hz, 3H; CH\(_3\)), 1.12-1.38 (m, 8H; CH\(_2\)), 1.48-1.50 (m, 2H; CH\(_2\)), 3.45-3.49 (m, H; CH\(_2\)). Data were according to the literature.\textsuperscript{23}

### 5.5 References


16 This result was not reproducible.

17 This catalyst was used in thiocarbonyl-boronic acid couplings, see: Liebeskind, L. S.; Srogl, J. J. Am. Chem. Soc. 2000, 122, 11260.


