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Further studies in the acyl-type radical additions promoted by SmI_2: mechanistic implications and stereoselective reduction of the keto-functionality

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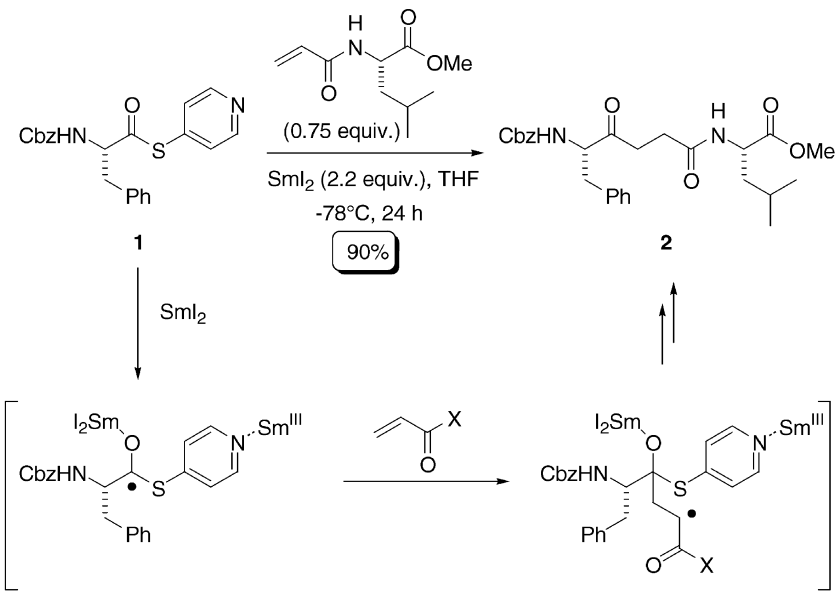
Abstract—Attempts were made to promote the carbonyl coupling of cyclohexanone to 4-pyridylthioesters of *N*-carbamate-protected amino acids with the one electron reducing agent, samarium diiodide. Such reactions proved unsuccessful due to the inability of the ketyl-type radical anion intermediate to be reduced to the corresponding dianion at −78°C. Nevertheless, these results explain our recently published work on the high efficiency of the SmI_2-mediated acyl-type radical additions of the same thioesters with electron deficient alkenes [*J. Am. Chem. Soc.* **2003**, *125*, 4030]. A study was also undertaken to examine methods for the stereoselective reduction of *N*-carbamate-protected amino ketones to either the *syn*- or *anti*-vicinal amino alcohols. In most cases, $LiAl(O\text{-}t\text{-}Bu)_3H$ and (*S*)-Alpine-Hydride were found to effectively provide the *anti*- and *syn*-amino alcohols, respectively. The SmI_2-promoted reduction of the same ketones afforded a majority of the *syn*-isomer with selectivities of approximately 5:1. However, in one case, the SmI_2-promoted reduction was found to be more effective than that of (*S*)-Alpine-Hydride.

1. Introduction

In a recent publication, we reported a novel radical addition reaction involving the samarium diiodide-mediated coupling of amino acid thioesters such as **1** to α,β-unsaturated amides and esters (Scheme 1).[1] Our interest in this carbon–carbon bond forming step is two-fold. First, this coupling reaction represents a novel route to peptide



Scheme 1.

Keywords: acyl-like radicals; stereoselective reductions; samarium diiodide; peptide mimics.
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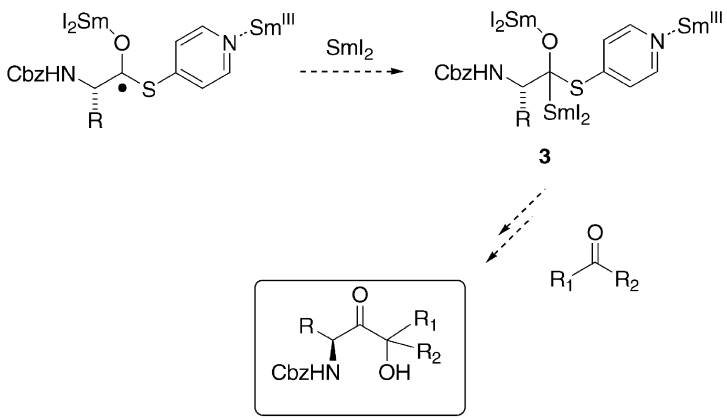


Scheme 2.

structures being closely related to a series of medicinally important proteinase inhibitors.[2] Second, the structures of the products formed composed of a γ-ketoamide or -ester as in **2** suggest the involvement of an acyl radical intermediate, which under normal circumstances would undergo a fast decarbonylation owing to the presence of the heteroatom in the α-position (Scheme 1).[3] That indeed decarbonylation is not detected indicates that an equivalent to the acyl radical is being generated under these reducing conditions, which is unable to undergo the decarbonylation step. In order to explain these results, we proposed a mechanism involving the reduction of the thioester via single electron transfer from the divalent lanthanide reagent directly into the C–O double bond, thereby generating a thio-substituted ketyl radical anion complexed to Sm(III).[1] Its subsequent coupling to an α,β-unsaturated amide or ester would then generate a metalated *S*,*O*-hemiketal. Collapse of this hemiketal intermediate with the eventual formation of a ketone under the reaction conditions was avoided by maintaining the reaction at low temperature (−78°C). This was necessary as the ketone itself could suffer a second SmI_2-mediated reduction.[4]

With these results in hand, we speculated whether the olefin-based radical acceptor could be replaced with a carbonyl substrate. In such a scenario, the ketyl-like radical intermediate formed after the first electron transfer would possibly be subjected to a second reduction step generating a dimetalated dianion **3** (Scheme 2). Its coupling to a ketone or aldehyde would eventually provide a new route to α-amino, α′-hydroxyketones, being an important precursor to 1-amino-2,3-diols (Scheme 2).[5] Particularly interesting are the stereochemical issues of the coupling step.

In this paper, we reveal our efforts for promoting the coupling of the amino acid thioesters to carbonyls with samarium diiodide. Although we have not been successful in achieving this goal, our results reveal interesting features pertaining to the mechanism of the radical coupling reactions. In the second part of this paper, we also report on the stereoselective reduction of the keto group in compounds such as **2** to provide either the *syn*- or *anti*-1,2 amino alcohol, which are again important structural entities of a series of proteinase inhibitors. The ability to selectively reduce this functionality would make this two-step radical addition/reduction sequence a viable approach to such inhibitors.

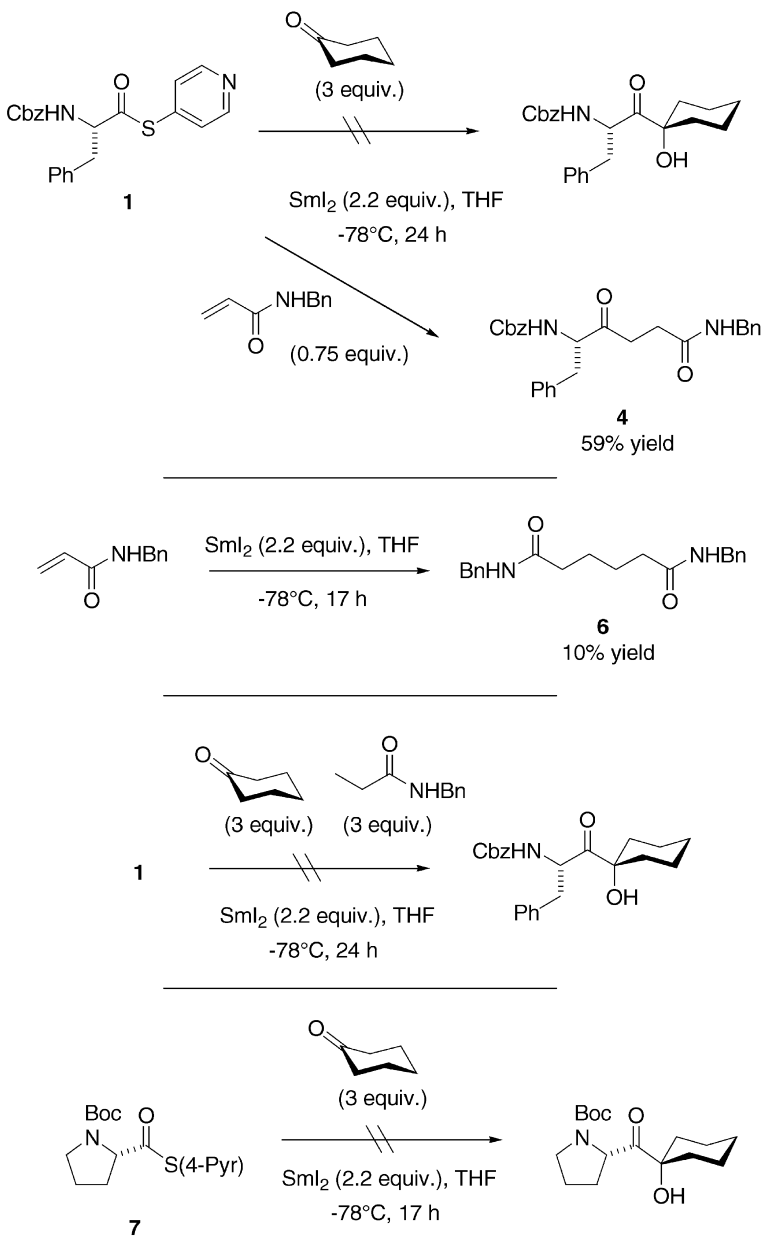
2. Results and discussion

2.1. Anionic coupling studies

Initial attempts to couple the 4-pyridyl thioester of Cbz-protected phenylalanine (**1**)[1] with carbonyl compounds were performed with cyclohexanone under the conditions reported for the radical addition reactions (Scheme 3). A solution of both compounds in THF was slowly added to a 0.1 M solution of SmI_2 in the same solvent cooled to −78°C. Unexpectedly, work up of the reaction mixture after 24 h and ^{1}H NMR analysis of the crude product revealed this to comprise mainly of the starting thioester contaminated with minor amounts of the amide of Cbz-protected phenylalanine. The latter compound originates from the thioester upon quenching of the reaction mixture with an aqueous ammonium chloride solution. Extending the reaction time even up to 66 h, did not change the outcome. Attempts to heat the reaction mixture to higher temperatures (up to 0°C) led to consumption of the divalent lanthanide reducing agent, but unfortunately also to multiple product formation as determined by thin-layer chromatography (TLC) analysis which were difficult to purify. Nevertheless, at higher temperatures electron transfer appeared to take place. Increasing the reducing power of the lanthanide(II) reagent by the addition of HMPA[6] or LiCl[6e,7] only led to extensive decomposition as monitored by TLC analysis.

Two parallel reactions were also carried out involving the coupling of **1** to either cyclohexanone and *N*-benzyl acrylamide at −78°C in separate flasks employing the same batch of thioester and etheral SmI_2 solution. In the latter case, the radical coupling reaction performed exactly as earlier reported, provided the ketone **4** in a 59% yield after a reaction time of only 24 h.

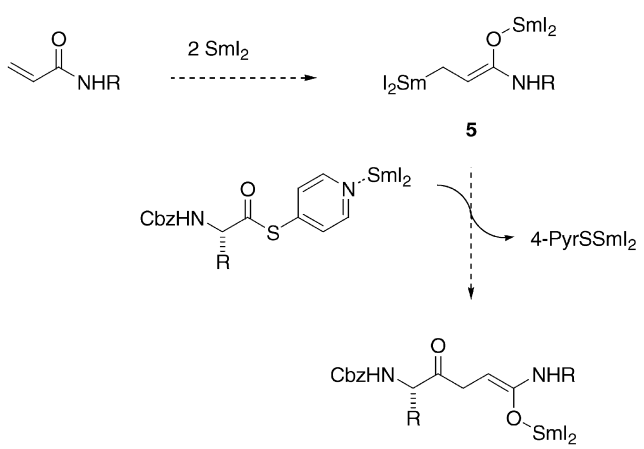
These simple experiments clearly demonstrate that the dianion **3** is not being produced upon subjection of the thioester to a ketone and SmI_2 at −78°C, which seems to contradict our previous postulation that the same thioester is



Scheme 3.

reduced to a ketyl radical anion equivalent under similar conditions in the presence of an electrophilic alkene.[1] There are two possible mechanistic scenarios which explain these observations, taking into respect our previous work on the radical addition reactions. The first one involves a reversible but endergonic reduction of the thioester by the single electron reducing agent.[6e,8] The subsequent trapping of the intermediate ketyl radical anion by a second equivalent of SmI_2 is unfavorable and hence starting material may be recovered in the absence of a radical acceptor.

As an alternative mechanism, perhaps the initial reduction step of the thioester is not operating at all. Instead, the known sequential reduction of the acrylamide with two equivalents of SmI_2 leads to the dianion **5** which can then participate in a nucleophilic acyl substitution with the activated thioester, as shown in Scheme 4. The C–C bond

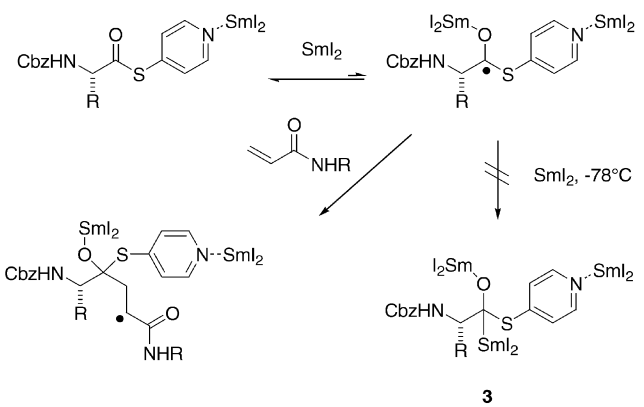


Scheme 4.

forming event is therefore anionic and not radical. However, this latter mechanism was eventually ruled out as subjection of *N*-benzyl acrylamide to excess SmI_2 for 17 h at −78°C afforded mainly unreacted starting material along with approximately 10% of the dimerization product **6** (Scheme 3).[9]

In order to examine the possible influence of the electron donating capacity of the CONH function in the acrylamide on the reducing properties of SmI_2, an anionic coupling reaction between **1** and cyclohexanone was also attempted in the presence of *N*-benzyl propionamide (Scheme 3). Yet again, only starting material and the corresponding amide were furnished. Finally, a similar carbonyl coupling reaction between the 4-pyridylthioester of *N*-Boc-protected proline (**7**) and cyclohexanone was performed in order to examine the outcome of this reaction with variations of the amino acid structure. However, once more unreacted starting material was the dominant product.

With these results in hand, we are led to the conclusion that the treatment of the 4-pyridylthioesters of amino acids with



Scheme 5.

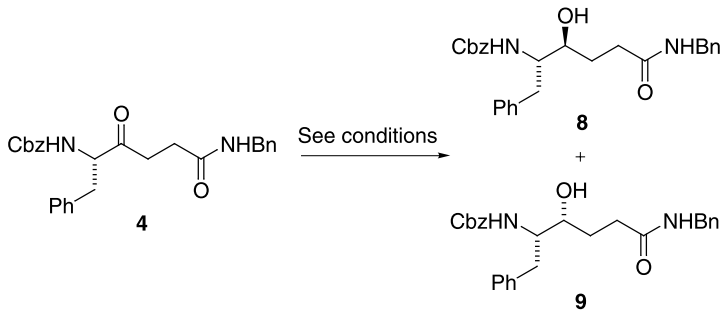
SmI_2 results in a reversible reduction step and formation of a ketyl-type radical anion coordinated to the metal ion in a low concentration (Scheme 5). Because the reduction of this radical to the corresponding dianion by a second equivalent of SmI_2 is unfavored at −78°C, this assures efficient coupling of the radical to the electron deficient alkenes without side reactions resulting in over-reduction of this initial radical. The reason for the lack of the second reduction step may lie in the relatively unfavored encounter between the bulky ketyl-type radical with the hepta-coordinated lanthanide reagent, $SmI_2(THF)_5$,[10] as the reduction step most likely will occur via inner-sphere electron transfer.

2.2. Ketone reduction studies

In order to increase the synthetic utility of the radical addition reactions leading to the preparation of δ-amino-γ-keto esters and amides, a small study was undertaken to examine methods for the stereoselective reduction of the ketone group to either the *syn*- or *anti*-vicinal amino-alcohols. The resulting δ-amino-γ-hydroxy esters and amides represent important substructures of the known HIV and renin aspartic proteinase inhibitors.[11,12] In 2002, two papers reported an extensive study of the reduction of *N*-carbamate-protected amino ketones.[13,14] The work in this paper exploits these results for the selective preparation of both amino alcohol diastereomers.

In principle, the alcohols could be obtained by a second reduction sequence of the ketone with SmI_2 under the condition of the radical addition reaction. Previous results demonstrated that indeed this was the case when the coupling reactions were run at higher temperatures and in the presence of a proton source.[15] The higher temperatures are required to liberate the ketone group from the metalated hemithioacetal. Nevertheless, the diastereoselectivity of the reduction step remained low (approximately 2:1). In contrast, subjecting the ketone **4** to 2 equiv. of SmI_2 with

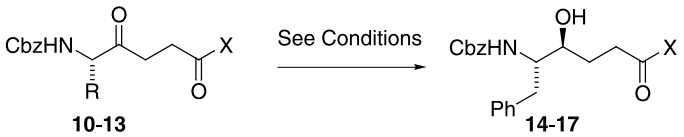
Table 1. Reduction studies with the ketone **4**



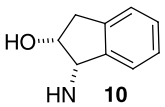
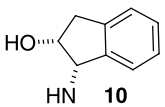
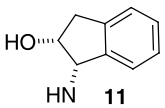
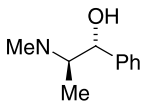
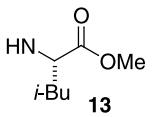
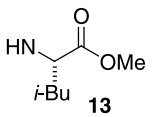
Entry	Conditions	Ratio **8**:**9**[a]	Yield
1	SmI_2 (4 equiv.) *t*-BuOH (1.5 equiv.) THF, 20°C, 17 h	5:1	58%
2	SmI_2 (4 equiv.) HMPA (20 equiv.) THF, −78°C, 17 h	4:1	59% (86%)[b]
3	$NaBH_4$, EtOH, −78°C	4:3	n.d.[c]
4	DIBALH, THF, −78°C	7:5	n.d.[c]
5	L-Selectride, THF, −78°C	1:1	n.d.[c]
6	$LiAl(O\text{-}t\text{-}Bu)_3H$, EtOH, −78°C	0:1	60%
7	(*S*)-Alpine-Hydride, THF, −78°C	1:0	71%

[a] Ratios based on ^1H NMR spectrum of crude product mixture.
[b] Yield based on recovered starting material.
[c] Not determined.

Table 2. Reduction studies with (*S*)-Alpine-Hydride



10-13 **14-17**

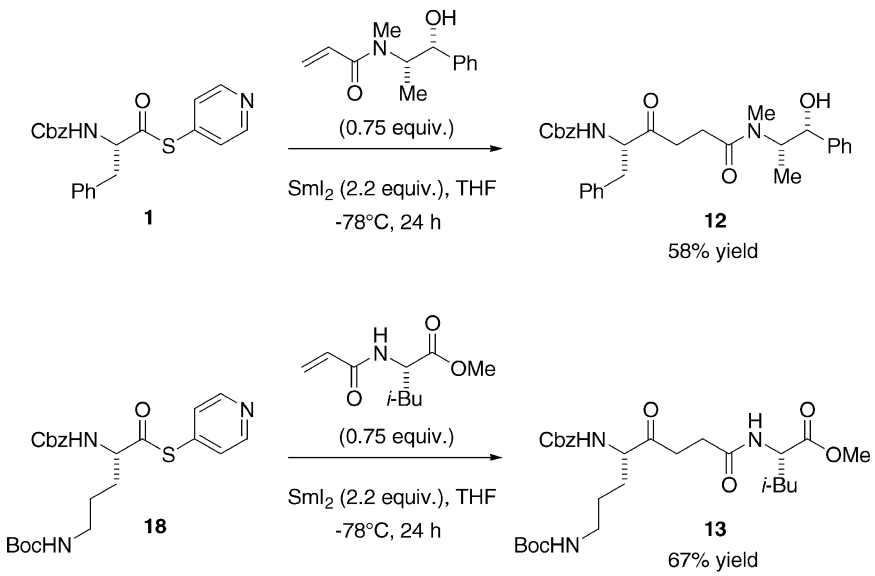
Entry	R	X	Conditions	Compound (yield)[a]
1	CH_2Ph	 **10**	SmI_2, *t*-BuOH	**14** (61%) (1:1)[b]
2	CH_2Ph	 **10**	(*S*)-Alpine-Hydride	**14** (69%)
3	*i*-Pr	 **11**	(*S*)-Alpine-Hydride	**15** (60%)
4	CH_2Ph	 **12**	(*S*)-Alpine-Hydride	**16** (75%)
5	$(CH_2)_3NHBoc$	 **13**	(*S*)-Alpine-Hydride	**17** (38%) (2:1)[b]
6	$(CH_2)_3NHBoc$	 **13**	SmI_2, *t*-BuOH	**17** (28%)

[a] Yields based on chromatographically pure compounds.
[b] Diastereomeric ratio.

t-BuOH for 17 h and at room temperature resulted in the selective formation of the *syn*-diastereromer **8** (Table 1, entry 1). Not surprisingly, the ligand composition on the lanthanide metal ion is not the same in the two cases, possibly explaining the deviation in the stereoselectivity for the two reactions. The influence of the *t*-BuOH on the diastereoselectivity proved non-existant, as the same diastereoselectivity was obtained in the absence of the alcohol. These reductions proved also to be rather slow at 20°C, however, when the strong electron donating ligand HMPA was added the reaction temperature could be considerably lowered. Somewhat unexpected though was the little change in the *syn*:*anti*-selectivity (entry 2).

The more traditional hydride-based reducing agents, including $NaBH_4$, DIBALH, and L-Selectride afforded essentially no selectivity in the ketone reduction (entries 3–5). Recently, Hoffman and co-workers reported LiAl(O-*t*-Bu)$_3$H in ethanol as an excellent reducing agent for the conversion of *N*-carbamate-protected amino ketones to *anti*-amino alcohols.[13] A model based on chelation control was used to explain this selectivity. Employing these conditions on **4** afforded a single amino alcohol in a 60% yield, which was tentatively assigned the *anti*-product **9** according to Hoffman's work (entry 7). In contrast, Luthman et al. have reported the reduction of similar amino ketones under Felkin–Ahn control affording the *syn*-amino alcohols.[14] In this work, (*S*)-Alpine-Hydride and NB-Enantride proved to be the most effective. Subjection of 2.5 equiv. of the former to the ketone **4** in THF at −78°C provided a single diastereomer according to ^{1}H NMR analysis of the crude reaction mixture, which was identical to the major isomer obtained from the SmI_2-mediated reductions (entry 8). Chromatographic purification provided the *syn*-diastereomer **8** in a 71% yield.

The generality of the *syn*-selectivity was tested on a few other substrates obtained from the radical addition reactions as illustrated in Table 2. The starting ketones for entries 1–3 were at our disposal from our previous work.[1] On the other hand, two other ketones used for this study (entries 4 and 5) were prepared from the acyl-like radical coupling reaction as shown in Scheme 6. Treatment of the thioester **1** with the acrylamide derivative of (1*R*,2*R*)-pseudoephedrine in the presence of SmI_2 at low temperature for 40 h provided the ketone **12** in an acceptable yield of 58% (Scheme 6). The successful coupling onto the acrylamide was pleasing as the use of this chiral auxiliary could potentially allow for the stereoselective introduction of substituents at the C2-position according to the earlier work of Myers.[16] The ability to correctly functionalize the C2-carbon is a prerequisite for the adaptation of the radical coupling step



Scheme 6.

to the synthesis of the known HIV and renin aspartic proteinase inhibitors.[11,12] Similarly, the coupling of the α-*N*-Cbz- and γ-*N*-Boc-protected ornithine thioester **18** with the acrylamide of leucine furnished the tripeptide mimic **13**, Orn-Gly-Leu, in a good yield of 67% (Scheme 6). Interestingly, it was necessary to prolong the reaction time to 80 h in order to obtain an acceptable yield of the coupling product. It is surprising how this subtle change in the structure of the thioester can lower the rate of coupling step by two-fold and clearly calls for further studies in order to improve this radical carbon, carbon bond forming reaction.

Reduction of the ketones illustrated in Table 2 with (*S*)-Alpine-Hydride required 5–6 equiv. of the reducing agent. Nevertheless, the selectivity and yield proved tolerant to the presence of a hydroxy group in the amide substituent of ketones **10**–**12** (entries 2–4). The SmI_2-mediated reduction was less effective with these substrates as shown by the 1:1 selectivity obtained upon the reduction of the amino ketone **10** depicted in entry 1. However, a complete reversal in the selectivities was observed with the amino ketone **13** (entry 5). In this case, essentially no *syn*-selectivity could be achieved with the chiral boron hydride reducing agent (d.s.=2:1). On the other hand, reduction with the low valent lanthanide reagent afforded stereospecifically a single stereoisomer although in modest yield (entry 6) which was identical to the major diastereomer obtained from the Alpine-Hydride reduction. The relative configuration of the amino alcohol has only been tentatively assigned, as attempts to cyclize the compound to its corresponding oxazolidinone as described by Hoffman[13] were met with extensive decomposition. The culprite for this stereochemical divergence is most likely the *N*-Boc-protected amine of the side chain in **13**.

3. Conclusion

In conclusion, attempts were made to promote the carbonyl coupling of cyclohexanone to 4-pyridylthioesters of *N*-carbamate-protected amino acids in the presence of samarium diiodide. Whereas these anionic coupling reactions were unsuccessful, this work suggests that the intermediate ketyl-type radical anion is not reduced to the dianion with SmI_2 at −78°C. This inability for reduction may explain the relatively high yields of the radical addition reactions. Finally, a small study was undertaken to examine methods for the stereoselective reduction of the *N*-carbamate-protected amino ketones to either the *syn*- or *anti*-vicinal amino alcohols. The previously reported reduction conditions employing $LiAl(O\text{-}t\text{-}Bu)_3H$ and (*S*)-Alpine-Hydride were found to effectively provide the *anti*- and *syn*-amino alcohols. However, in one case, SmI_2 was found to provide the best selectivities in the reduction step. Further work is now underway to exploit this two step radical addition, reduction sequence to the synthesis of specific proteinase inhibitors.

4. Experimental

4.1. General

Unless otherwise stated, all reactions were carried out under argon. THF was dried and freshly distilled over sodium/benzophenone. Ethanol (99.9%) was dried over 4 Å molecular sieves. Reactions were monitored by TLC analysis. The *N*-carbamate-protected amino ketones used in this study were synthesized as previously described.[1] Samarium diiodide was prepared according to the literature.[17]

4.1.1. (4*S*,5*S*)-*N*-Benzyl-5-benzyloxycarbonylamino-6-phenyl-4-hydroxy-hexane amide (8). General procedure for the reduction with (*S*)-Alpine-Hydride. The ketone **4** (30 mg, 0.068 mmol) was dissolved in dry distilled THF (2 mL) under nitrogen and cooled to −78°C. (*S*)-Alpine-Hydride (lithium *B*-isopinocamphenyl-9-borabicyclo-[3.3.1]nonyl hydride, 338 μL, 0.50 M in THF, 2.5 equiv.) was slowly added over 5 min. After stirring for 2.5 h at −78°C, the reaction was quenched by the addition of aqueous HCl (0.5 mL, 0.5 M) and extracted with EtOAc,

washed with water, dried and concentrated in vacuo. NMR analysis of the crude reaction mixture revealed only the (*S*)-alcohol reduction product. Column chromatography (EtOAc–pentane, 1:1–3:1) afforded 21 mg of **8** (71% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35–7.21 (m, 15H), 5.92 (br t, 1H, J=6.0 Hz), 5.28 (br d, 1H, J=9.2 Hz), 5.06 (d, 1H, J=12.4 Hz), 5.00 (d, 1H, J=12.4 Hz), 4.65 (d, 1H, J=2.8 Hz), 4.39 (d, 2H, J=6.0 Hz), 3.79 (dt, 1H, J=7.6, 8.0 Hz), 3.60 (m, 1H), 2.92 (d, 2H, J=9.6 Hz), 2.43–2.28 (m, 2H), 1.94–1.85 (m, 1H), 1.70–1.67 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.0, 156.8, 138.6, 138.0, 136.8, 129.6–126.6 (multiple peaks, 15C), 71.4, 66.8, 57.0, 44.1, 39.1, 33.9, 30.4. HRMS $C_{27}H_{30}N_2O_4$ [M+Na$^+$]; calculated: 469.2103, found: 469.2094.

4.1.2. (4*S*,5*S*)-*N*-Benzyl-5-benzyloxycarbonylamino-6-phenyl-4-hydroxy-hexane amide (9). $LiAl(O\textit{t}\text{-}Bu)_3H$ (102 mg, 0.405 mmol) was flushed with nitrogen and cooled to −78°C. EtOH (2 mL) was slowly added along the side of the flask to keep the temperature below −50°C followed by a solution of the ketone **4** (30 mg, 0.068 mmol) in EtOH (1 mL). After stirring for 2 h at −78°C, the reaction was quenched by the addition of aqueous HCl (0.5 mL, 0.5 M) and extracted with EtOAc, washed with water, dried and concentrated in vacuo. NMR analysis of the crude reaction mixture revealed only the (*R*)-alcohol reduction product. Column chromatography (EtOAc–pentane, 1:1–2:1) afforded the alcohol **9** (18 mg, 60% yield) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36–7.13 (m, 15H), 5.92 (br s, 1H), 5.00 (s, 2H), 4.87 (br d, 1H, J=8.8 Hz), 4.44 (d, 2H, J=5.6 Hz), 4.41 (br d, 1H, J=4.4 Hz), 3.91 (m, 1H), 3.68 (m, 1H), 2.98 (dd, 1H, J=4.8, 14.4 Hz), 2.84 (dd, 1H, J=9.2, 14.4 Hz), 2.50–2.42 (m, 2H), 1.90 (m, 1H), 1.82 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.8, 156.8, 138.1, 136.6, 129.0 (2C), 128.7 (2C), 128.3, 128.1 (2C), 127.9, 126.7, 73.7, 66.9, 57.1, 44.1, 33.6, 29.9, 28.8. HRMS $C_{27}H_{30}N_2O_4$ [M+Na$^+$]; calculated: 469.2103, found: 469.2112.

4.1.3. Reduction of ketone 4 with SmI_2 and *t*-BuOH. To a solution of the ketone **4** (30 mg, 0.068 mmol) and *t*-BuOH (8 μL, 0.084 mmol) in dry distilled THF (2 mL) was added SmI_2 (2.8 mL, 0.10 M, 0.284 mmol) under an argon atmosphere, and the reaction mixture was stirred overnight at 20°C. Excess SmI_2 was oxidized by bubbling oxygen through the solution until a yellow color was obtained. Saturated aqueous NH_4Cl (0.5 mL) was added and the organic solvent was removed by evaporation. CH_2Cl_2 was added and the organic phase was washed with water and brine, dried and concentrated in vacuo. NMR analysis of the crude reaction mixture revealed the two reduction products in an *syn*:*anti* ratio of approx. 5:1. Column chromatography (EtOAc–pentane, 1:1–2:1) afforded 17.4 mg of the alcohols **8** and **9** (58% yield) as a colorless solid.

4.1.4. (5*S*)-*N*-Methyl-*N*-((1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl)-5-benzyloxycarbonylamino-4-oxo-6-phenyl-hexane amide (12). A solution of the 4-pyridyl thioester of Cbz-protected phenylalanine[1] (706 mg, 1.80 mmol) and *N*-((1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-acrylamide (263 mg, 1.20 mmol) in THF (10 mL) was added dropwise over 15 min via syringe pump to a solution of SmI_2 in THF (0.1 M, 40 mL, 4.0 mmol) cooled to −78°C, and the solution was left stirring at this temperature for 40 h. The excess SmI_2 was oxidized by flushing the mixture with oxygen from a balloon. To the now yellow solution was added satd. aqueous NH_4Cl at −78°C followed by warming to room temperature. The THF was evaporated off and 0.5 M $HCl_{(aq)}$ was added followed by extraction with EtOAc (3×). The combined organic phases were washed with $NaOCl_{(aq)}$ and brine, dried over $MgSO_4$ and then evaporated in vacuo. The coupling product was purified by flash chromatography on silica gel using CH_2Cl_2–MeOH (60:1) as the eluent, affording **12** as a colorless syrup (348 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) Mixture of rotamers; Only the major rotamer is assigned. 7.40–7.10 (15H, m), 5.50 (1H, br d, J=7.0 Hz), 5.09 (1H, d, J=11.9 Hz), 5.04 (1H, d, J=11.9 Hz), 4.65 (1H, q, J=7.0 Hz), 4.56 (1H, t, J=6.8 Hz), 4.47 (1H, quintet, J=6.8 Hz), 3.88 (1H, br s), 3.23 (1H, dd, J=7.0, 14.2 Hz), 2.99 (1H, dd, J=7.0, 14.2 Hz), 2.84 (3H, s), 2.79 (2H, t, J=7.2 Hz), 2.57 (2H, t, J=7.2 Hz), 1.05 (3H, d, J=6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 208.4, 208.0, 173.4, 172.5, 155.9, 155.9, 142.2–126.7 (multiple peaks, 36C), 76.3, 75.5, 66.9, 66.9, 60.9, 60.9, 58.4, 58.0, 37.2, 37.2, 35.4, 35.0, 32.1, 28.2, 27.5, 27.0, 15.4, 14.4. IR 3414, 3031, 2930, 1719, 1702, 1624, 1498 cm^{-1}. HRMS $C_{30}H_{34}N_2O_5$ [M+Na$^+$]; calculated: 525.2365, found: 525.2365.

4.1.5. (2*S*)-2-[(5*S*)-5-Benzyloxycarbonylamino-8-*tert*-butoxycarbonylamino-4-oxo-octanoylamino]-4-methyl-pentanoic acid methylester (13). A solution of the thioester **18** (185 mg, 0.40 mmol) and the acrylamide of leucine methyl ester (53 mg, 0.27 mmol) in THF (5.0 mL) was added dropwise over 15 min via syringe pump to a solution of SmI_2 in THF (0.1 M, 12 mL, 1.2 mmol) cooled to −78°C, and the solution was left stirring at this temperature for 80 h. The excess SmI_2 was oxidized by flushing the mixture with oxygen from a balloon. To the now yellow solution was added satd. aqueous NH_4Cl at −78°C followed by warming to room temperature. The THF was evaporated off and 0.5 M $HCl_{(aq)}$ was added followed by extraction with EtOAc. The combined organic phases were washed with $NaOCl_{(aq)}$ and brine, dried over $MgSO_4$ and then evaporated in vacuo. The coupling produc was purified by flash chromatography on silica gel using pentane–EtOAc (3:1–1:1) as the eluent, affording **13** as a yellow oil (98 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35 (s, 5H), 6.02 (br d, 1H, J=7.6 Hz), 5.59 (br d, 1H, J=7.2 Hz), 5.01 (s, 2H), 4.76 (br s, 1H), 4.59 (dt, 1H, J=8.8, 4.8 Hz), 4.43 (br q, 1H, J=4.4 Hz), 3.71 (s, 3H), 3.13 (d, 2H, J=10 Hz), 2.98–2.90 (m, 1H), 2.77–2.70 (m, 1H), 2.59–2.46 (m, 2H), 2.00–1.90 (m, 1H), 1.72–1.59 (m, 4H), 1.43 (s, 9H), 0.93 (d, 3H, J=5.2 Hz), 0.92 (d, 3H, J=4.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 208.1, 173.8, 171.4, 156.3 (2C), 136.5, 128.7 (2C), 128.4, 128.3 (2C), 79.3, 67.2, 59.5, 52.5, 51.0, 41.8, 40.2, 34.7, 29.6, 28.8, 28.6 (3C), 25.6, 25.0, 23.0, 22.1. HRMS $C_{28}H_{43}N_3O_8$ [M+Na$^+$]; calculated: 572.2948, found: 572.2932.

4.1.6. (4*S*,5*S*)-*N*-((1*S*,2*R*)-2-Hydroxy-indan-1-yl)-5-benzyl-oxycarbonylamino-6-phenyl-4-hydroxy-hexane amide (14). The alcohol **14** was prepared from the ketone **10** according to the general procedure outlined for **8**, with the following quantities: ketone **10** (30 mg, 0.062 mmol) and

6 equiv. of (*S*)-Alpine-Hydride (740 μL, 0.5 M in THF). Flash chromatography (EtOAc–pentane, 3:1) afforded **14** (20.7 mg, 69%) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.38–7.12 (m, 14H), 6.33 (br s, 1H), 5.57 (br s, 1H), 5.32 (dd, 1H, *J*=4.8, 8.0 Hz), 5.08 (d, 1H, *J*=12.4 Hz), 5.01 (d, 1H, *J*=12.4 Hz), 4.98 (br s, 1H), 4.60 (m, 1H), 4.46 (br s, 1H), 3.82 (dt, 1H, *J*=7.2, 8.4 Hz), 3.15 (dd, 1H, *J*=5.6, 16.0 Hz), 2.95–2.88 (m, 3H), 2.48 (m, 1H), 2.28 (m, 1H), 2.03 (m, 1H), 1.85 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.1, 156.8, 140.3–124.5 (multiple peaks, 18C), 73.2, 72.0, 66.8, 58.1, 57.2, 39.8, 38.8, 34.2, 30.6. HRMS $C_{29}H_{32}N_2O_5$ [M+Na$^+$]; calculated: 511.2202, found: 511.2222.

4.1.7. (4*S*,5*S*)-*N*-((1*S*,2*R*)-2-Hydroxy-indan-1-yl)-5-benzyloxycarbonylamino-7-methyl-4-hydroxy-octane amide (15). The alcohol **15** was prepared from the ketone **11** according to the general procedure outlined for **8**, with the following quantities: ketone **11** (31.5 mg, 0.070 mmol) and 5 equiv. of (*S*)-Alpine-Hydride (696 μL, 0.5 M in THF). Flash chromatography (EtOAc–pentane, 3:1) afforded **15** (19.0 mg, 60%) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36–7.23 (m, 9H), 6.39 (br d, 1H, *J*=8.0 Hz), 5.35 (dd, 1H, *J*=4.8, 8.0 Hz), 5.21 (br d, 1H, *J*=10.0 Hz), 5.09 (d, 1H, *J*=12.4 Hz), 5.04 (d, 1H, *J*=12.4 Hz), 4.94 (br d, 1H, *J*=8.4 Hz), 4.62 (m, 1H), 4.06 (br s, 1H), 3.82–3.61 (m, 2H), 3.15 (ddd, 1H, *J*=3.2, 4.8, 16.4 Hz), 2.93 (dd, 1H, *J*=1.2, 16.4 Hz), 2.56–2.34 (m, 2H), 1.88–1.81 (m, 2H), 1.6–1.60 (m, 1H), 1.39–1.27 (m, 2H), 0.92 (d, 3H, *J*=4.4 Hz), 0.90 (d, 3H, *J*=4.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) mixture of rotamers, 175.0, 174.5, 157.2, 157.1, 140.6, 140.5, 140.4 (2C), 136.8, 136.6, 128.8–124.6 (multiple peaks, 18C), 74.6, 74.5, 73.6, 73.4, 67.2, 67.0, 58.1, 58.0, 54.4, 53.8, 39.8 (2C), 36.6, 35.8, 34.3, 33.7, 30.6, 30.6, 23.8, 23.4, 22.4, 21.8, 20.2, 19.1. HRMS $C_{26}H_{34}N_2O_5$ [M+Na$^+$]; calculated: 477.2365, found: 477.2347.

4.1.8. (4*S*,5*S*)-*N*-Methyl-*N*-((1*R*,2*R*)-2-hydroxy-1-methyl-2-phenyl-ethyl)-5-benzyloxycarbonylamino-6-phenyl-4-hydroxy-hexane amide (16). The alcohol **16** was prepared from the ketone **12** according to the general procedure outlined for **8**, with the following quantities: ketone **12** (290 mg, 0.58 mmol) and 6 equiv. of (*S*)-Alpine-Hydride (7 mL, 0.5 M in THF, 3.5 mmol). Flash chromatography (EtOAc–pentane, 3:2–6:1) afforded **16** (220 mg, 75%) as a colorless syrup. Mixture of rotamers; major=a, minor=b: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.40–7.15 (m, 15Ha, 15Hb), 5.51 (br d, 1Hb, *J*=9.4 Hz), 5.35 (br d, 1Ha, *J*=9.4 Hz), 5.10–5.01 (m, 2Ha, 2Hb), 4.98 (br s, 1Ha or 1Hb), 4.67 (br s, 1Ha or 1Hb), 4.62–4.58 (m, 1Ha or 1Hb), 4.54–4.51 (m, 1Ha, 1Hb), 3.95 (dq, 1Ha or 1Hb, *J*=6.8, 7.1 Hz), 3.82–3.76 (m, 1Ha, 1Hb), 3.57–3.56 (m, 1Ha, 1Hb), 3.46 (br s, 1Ha, 1Hb), 2.96–2.79 (m, 2Ha, 2Hb), 2.90 (s, 3Ha), 2.81 (s, 3Hb), 2.58 (ddd, 1Ha or 1Hb, *J*=4.0, 7.2, 16.8 Hz), 2.53 (t, 2Ha or 2Hb, *J*=6.8 Hz), 2.31 (ddd, 1Ha or 1Hb, *J*=4.0, 9.2, 16.8 Hz), 2.04–1.81 (m, 1Ha, 1Hb), 1.70–1.61 (m, 1Ha, 1Hb), 0.99 (d, 3Ha, *J*=6.8 Hz), 0.94 (d, 3Hb, *J*=6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 176.0, 175.5, 156.7 (2C), 142.0, 141.3, 138.8, 138.6, 136.9, 136.8, 129.7–126.3 (multiple peaks, 30C), 76.3, 75.6, 71.5, 71.2, 66.7, 66.6, 58.8, 57.3 (3C), 39.1, 39.0, 32.0 (3C), 31.1, 30.1, 29.6, 15.5, 14.5. HRMS $C_{30}H_{36}N_2O_5$ [M+Na$^+$]; calculated: 527.2522, found: 527.2548.

4.1.9. (2*S*)-((4*S*,5*S*)-5-Benzyloxycarbonylamino-8-*tert*-butoxycarbonylamino-4-hydroxy-octanoylamino)-4-methyl pentanoic acid methyl ester (17). The alcohol **17** was prepared from the ketone **13** according to the procedure outlined in Section 4.1.3, with the following quantities: ketone **13** (32.9 mg, 0.06 mmol) and 4.2 equiv. of SmI_2 (2.5 mL, 0.1 M in THF). Flash chromotography (EtOAc–pentane, 5:1) afforded **17** (9.1 mg, 28%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 (m, 5H), 6.11 (br s, 1H), 5.16–5.05 (m, 3H), 4.62–4.57 (m, 2H), 4.08 (br s, 1H), 3.73 (s, 3H), 3.65 (br d, 1H, *J*=7.6 Hz), 3.59 (br d, 1H, *J*=7.6 Hz), 3.12 (br d, 2H, *J*=5.2 Hz), 2.45–2.39 (m, 2H), 1.89–1.79 (m, 1H), 1.78–1.69 (m, 2H), 1.66–1.61 (m, 2H), 1.6–1.49 (m, 2H), 1.43 (s, 9H), 0.93 (d, 6H, *J*=6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.9, 173.7, 157.0, 156.3, 136.8, 128.7 (2C), 128.3, 128.2 (2C), 79.3, 73.0, 66.9, 55.3, 52.6, 51.1, 41.7, 40.5, 33.6, 30.2, 30.1, 28.6 (3C), 26.9, 25.1, 23.0, 22.2. HRMS $C_{28}H_{45}N_3O_8$ [M+Na$^+$]; calculated: 574.3104, found: 574.3127.

4.1.10. (2*S*)-2-Benzyloxycarbonylamino-5-*tert*-butoxycarbonylamino-pentanethioic acid *S*-pyridin-4-yl ester (18). A solution of the α-*N*-Cbz- and δ-*N*-Boc-protected ornithine derivative (472 mg, 1.29 mmol) and 4-mercaptopyridine (144 mg, 1.29 mmol) in dry distilled dichloromethane (15 mL) was cooled to 0°C. EDC (296 mg, 1.54 mmol) was added and the solution was stirred for 10 min at 0°C and then warmed to 20°C followed by stirring for an additional 2 h. The solution was diluted with dichloromethane and then washed four times with water and once with brine. After drying (Na_2SO_4) and evaporation to dryness, the residue was purified by column chromatography (Pentane–EtOAc, 2:3) affording 338.4 mg (57% yield) of **18** as colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.63 (d, 2H, *J*=4.8 Hz), 7.39–7.33 (m, 7H), 5.68 (br s, 1H), 5.18 (s, 2H), 4.60 (br s, 1H), 4.54 (m, 1H), 3.16 (m, 2H), 1.97 (m, 1H), 1.73 (m, 1H), 1.68 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.4, 156.4, 156.3, 150.2, 138.6, 136.3, 128.8, 128.5, 128.4 (2C), 79.6, 67.6, 61.5, 40.0, 28.6 (3C), 26.6. HRMS $C_{23}H_{29}N_3O_5S$ [M+Na$^+$]; calculated: 482.1726, found: 482.1819.

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