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Date:
2021-01-21

Citation:
Shang, J., Thombare, V. J., Charron, C. L., Wille, U. & Hutton, C. A. (2021). Ring Expansion of Thiolactams via Imide Intermediates: An Amino Acid Insertion Strategy. Chemistry A European Journal, 27 (5), pp.1620-1625. https://doi.org/10.1002/chem.202005035.

**Author Manuscript**

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**To be cited as:** 10.1002/chem.202005035

**Link to VoR:** https://doi.org/10.1002/chem.202005035

COMMUNICATION

# Ring expansion of thiolactams via imide intermediates: an amino acid insertion strategy

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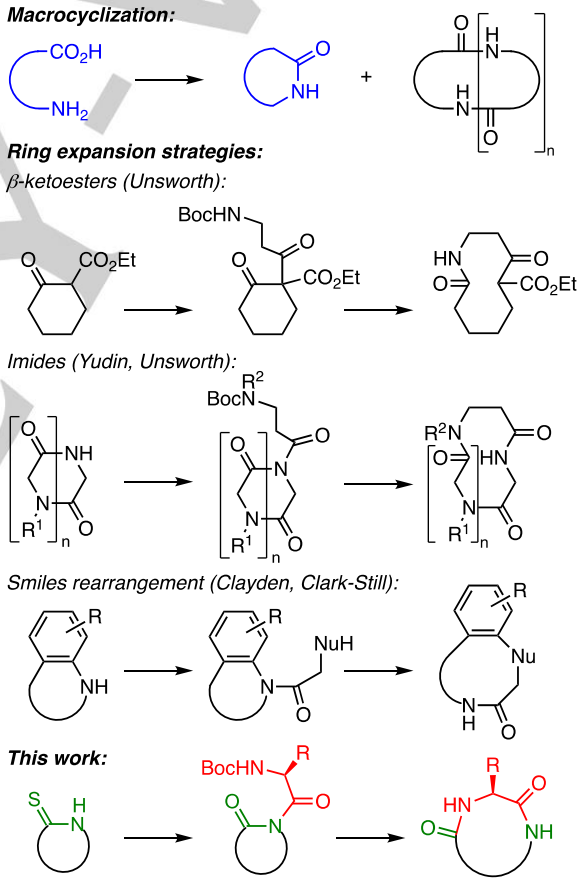
**Abstract:** The Ag(I)-promoted reaction of thiolactams with *N*-Boc amino acids yields an *N*-(α-aminoacyl) lactam that can rearrange through an acyl transfer process. Boc-deprotection results in convergence to the ring-expanded adduct, thereby facilitating an overall insertion of an amino acid into the thioamide bond to generate medium-sized heterocycles. Application to the site-specific insertion of amino acids into cyclic peptides is demonstrated.

Macrocycles such as cyclic peptides are typically constructed by head-to-tail cyclization, coupling the terminal amine and carboxylic acid groups.[1] However, medium-sized macrocycles are often not accessed efficiently via head-to-tail macrocyclization due to conformational constraints inherent in medium sized rings.[2-10] Macrocyclization can frequently lead to the formation of cyclodimers and higher oligomers and is therefore typically conducted under high dilution conditions.

In order to overcome conformational constraints and reduce the entropic barrier to macrocyclization inherent in medium-sized rings, ring expansion and ring contraction strategies have been developed.[11-13] An example of ring a contraction strategy reported by Smythe and co-workers incorporates an auxiliary which facilitates large ring formation, followed by contraction and ultimately extrusion of the auxiliary, to generate cyclic tetrapeptides.[14,15] Ring expansions of small rings have also been employed for the generation of medium-sized rings.[16] Notable examples include Unsworth's 'SuRE' method,[17,18] which appends an amino acid onto a cyclic β-ketoester: nucleophilic attack by the tethered *N*-nucleophile and ring opening results in overall insertion of an α- or β-amino acid into enlarged macrocycle (Scheme 1). Unsworth has applied this methodology to the ring expansion of lactams via imides, [19-21] and Yudin has incorporated β-amino acids into lactams and diketopiperazines via a similar process.[22] Yudin has also reported a site-selective formal ring expansion of aziridine-containing cyclic peptides,[23] whereas Clayden[24,25] and Clark-Still[26] have employed Smiles rearrangements to insert amino acid residues or urea derivatives into small *N*-aryl heterocycles.

One limitation of most current methods for ring expansion, particularly as applied to cyclic peptides, is site selectivity. The imide formation–acyl transfer process requires N-acylation of a single amide group within a cyclic peptide, which necessitates protection of all other secondary amides. In the original SuRE process the β-ketoester moiety confers chemoselectivity but introduces a non-peptide component into the macrocycle. Thus, the site-specific ring expansion of cyclic peptides remains a significant challenge.




**Scheme 1.** Ring expansion strategies for macrocycle synthesis.

We have previously shown that thioamides can undergo a Ag(I)-facilitated coupling reaction with amino acids to generate imides,[27,28] and that such *N*-(α-aminoacyl) amide adducts undergo facile acyl transfer processes.[10,27,29] We envisaged that elaboration of this coupling reaction to cyclic systems – i.e. thiolactams – would lead to an overall insertion process (Scheme 1). Herein we report the development of a ring expansion process that enables the site-specific insertion of an amino acid residue

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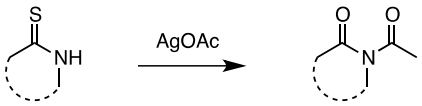
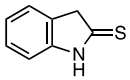
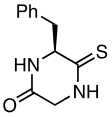
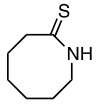
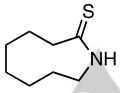
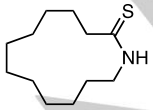
into a thiolactam, or cyclic peptide thioamide, via an imide intermediate.

To date, the Ag(I)-promoted conversion of thioamides to imides has not been performed on cyclic systems:[27,30,31] accordingly, we first investigated whether thiolactams are viable starting materials in this transformation. The simple thiolactams **1**–**8** were first prepared from the corresponding lactams by treatment with Lawesson's reagent, and their conversion to *N*-acetyl imides through reaction with AgOAc was investigated. Surprisingly, 5- and 6-membered thiolactams **1**–**4** (including thioketopiperazines) did not undergo transformation to the corresponding imides, instead undergoing reversion back to the lactam (Table 1, entries 1–4). Nevertheless, caprothiolactam **5** did generate the corresponding imide in low yield (Table 1, entry 5). Larger ring thiolactams **6**–**8** generated the corresponding imides in moderate to good yields (Table 1, entries 6–8).

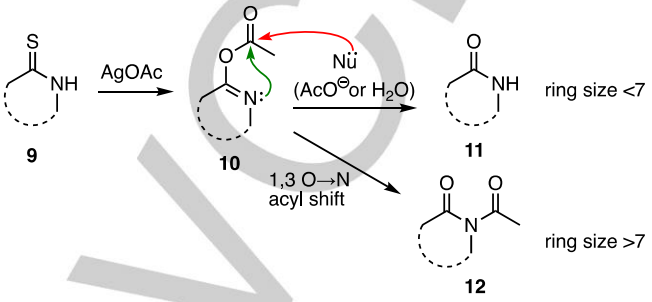
**Table 1.** Imide formation from thiolactams.[a]




| Entry | Substrate | | Yield of imide (%) |
|---|---|---|---|
| 1 |  | **1** | – |
| 2 |  | **2** | – |
| 3 |  | **3** | – |
| 4 |  | **4** | – |
| 5 |  | **5** | 20 |
| 6 |  | **6** | 54 |
| 7 |  | **7** | 55 |
| 8 |  | **8** | 78 |

[a] Reaction Conditions: thiolactam (0.5 mmol), AgOAc (1.0 mmol) in $CH_2Cl_2$ (2 mL), rt 18 h.

The Ag(I)-promoted conversion of thioamides **9** to imides **12** in the presence of carboxylic acids proceeds via an isoimide intermediate **10**.[28] The isoimide **10** then undergoes a pseudo-pericyclic 1,3-acyl transfer to generate the imide **12**. The efficiency of the 1,3-acyl transfer has been shown to be intricately controlled by competing steric and electronic factors.[28,29,32,33] We presumed that the failure of the 5- and 6-membered thiolactams to generate the corresponding imides was a result of an unfavourable 1,3-acyl transfer that must proceed through a strained 4,5- (or 4,6-) bicyclic transition state. In such strained systems where 1,3-acyl transfer is slow, the isoimide **10** could undergo reaction with a nucleophile, such as acetate or water, to generate the lactam **11** (Scheme 2).




**Scheme 2.** Isoimide rearrangement to imide or hydrolysis to amide.

To provide support for this hypothesis, computational analysis was performed for selected reaction systems at the M062X/6-31+G* level of theory in dichloromethane (Figure 1).[34-38]} The 1,3-acyl transfer of the isoimide derived from pyrrolidine-2-thione **1** requires an activation energy of 118.6 kJ $mol^{-1}$, which is too high to proceed under ambient conditions. The equivalent process in the six-, seven-membered or eight-membered isoimide is obviously facilitated by an increased conformational flexibility, which leads to a gradual reduction of the barrier by up to 30 kJ $mol^{-1}$. This finding is reflected in the geometry of the transition states, which shows for the smallest ring system a nearly symmetrical arrangement of the migrating acyl moiety and the *O*- and *N*-reaction centres (Figure 2a). In contrast, the transition state structures for the larger substrates are not only more compact but are also slightly unsymmetrical with the *O*-acyl distance being shorter by ca. 0.2 Å compared with the *N*-acyl distance for the seven- and eight-membered ring system, which is in-line with an earlier transition state. The particularly high barrier for the smallest ring system ($n$ = 1) is likely due to a nearly planar and therefore strained five-membered ring (Figure 2b). Increasing ring size leads to a more flexible and less strained geometry, which results in a lower barrier for the 1,3-acyl transfer.

Interestingly, although this rearrangement is exothermic in all cases, it is thermodynamically most preferable for the smallest ring system. This finding could be rationalized by a reduction of ring strain in the 5-membered imide, compared with the isoimide, that allows a more staggered arrangement of the methylene groups in the ring. Overall, these data clearly indicate that the 1,3-acyl migration is a kinetically driven process.

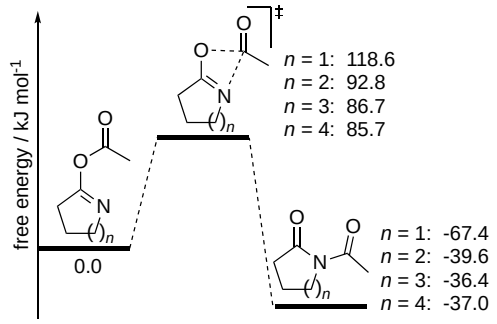



**Figure 1.** Potential energy surface for the rearrangement of isoimides to imides through 1,3-acyl transfer calculated with M062X/6-31+G* in dichloromethane.

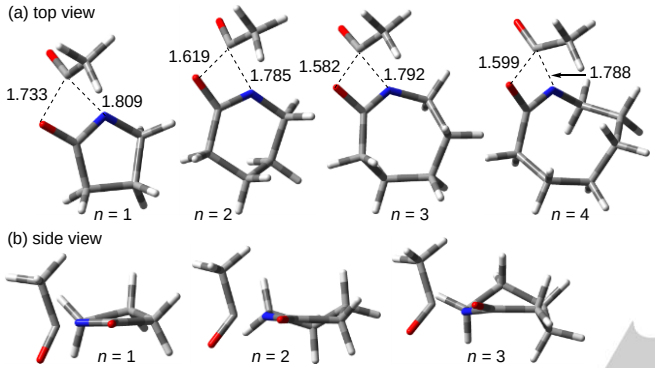
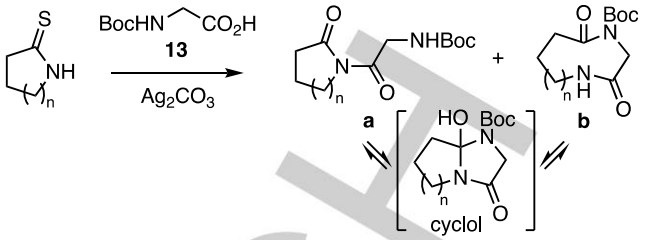



**Figure 2.** Calculated transition state geometries for the 1,3-O–N acyl transfer from isoimides generated from 5-, 6-, 7- and 8- membered thiolactams (with selected geometrical data (in Å; M062X/6-31+G*; in dichloromethane)).

With the results of the model reactions of thiolactams with AgOAc in hand, coupling reactions with Boc-glycine **13** as the acid component were next undertaken (Table 2). Reactions of the 5- and 6-membered pyrrolidine-2-thione **1** and piperidine-2-thione **3** with Boc-glycine **13** in the presence of silver carbonate did not furnish any imide adducts (Table 2, entries 1,2), in accordance with previous observations. Treatment of the 7-membered caprothiolactam **5** generated the imide **14a** in low yield after 18 h (Table 2, entry 3). After 48 h, the yield of the imide **14a** had increased, and notably the ring expanded product **14b** was also formed, with a combined yield of **14a** and **14b** of 69% (Table 2, entry 4). The structures of isomeric **14a** and **14b** were confirmed by 1D and 2D $^{1}$H-NMR spectroscopy, which demonstrated coupling between the carbamate NH and glycinyl $CH_2$ group in imide **14a** and the lack of such coupling in **14b**. Thus, the formation of the initial imide product **14a** is accompanied by a slow rearrangement/ring expansion to generate the glycine-inserted medium-sized cyclic product **14b** via the 'cyclol' intermediate. [22] Extended reaction times beyond 48 h did not increase the proportion of the ring expanded adduct **14b** further.

Treatment of the 8-membered thiolactam **6** under the same conditions afforded the imide **15a** in 38% yield after 18 h, together with 17% yield of ring-expanded imide **15b** (Table 2, entry 5). After 48 h, the proportions of imide **15a** and ring expanded imide **15b** were virtually unchanged (Table 2, entry 6).

**Table 2.** Reaction of thiolactams with Boc-Gly **13** + $Ag_2CO_3$.[a]




| Entry[a] | thiolactam | n | time | Yield **a** (%) | Yield **b** (%) |
|---|---|---|---|---|---|
| 1 | **1** | 1 | 18 h | 0 | 0 |
| 2 | **3** | 2 | 18 h | 0 | 0 |
| 3 | **5** | 3 | 18 h | **14a**, 16 | **14b**, 0 |
| 4 | | | 48 h | **14a**, 39 | **14b**, 30 |
| 5 | **6** | 4 | 18 h | **15a**, 38 | **15b**, 17 |
| 6 | | | 48 h | **15a**, 36 | **15b**, 18 |
| 7 | **7** | 5 | 18 h | **16a**, 37 | **16b**, 19 |
| 8 | | | 48 h | **16a**, 1 | **16b**, 88 |
| 9 | **8** | 9 | 18 h | **17a**, 69 | **17b**, 25 |
| 10 | | | 48 h | **17a**, 65 | **17b**, 31 |

[a] Reaction conditions: thiolactam (0.2 mmol), Boc-Gly **13** (0.1 mmol), $Ag_2CO_3$ (0.2 mmol) in $CH_2Cl_2$ (2 mL), rt 18–48 h.

Reaction of the 9-membered caprylothiolactam **7** furnished the imide **16a** and ring-expanded product **16b** in reasonable combined yield after 18 h (Table 2, entry 7). After 48 h, in contrast to the 7- and 8-membered systems, essentially all the initial imide **16a** had rearranged to the ring-expanded system **16b**, which was isolated in excellent yield (Table 2, entry 8).

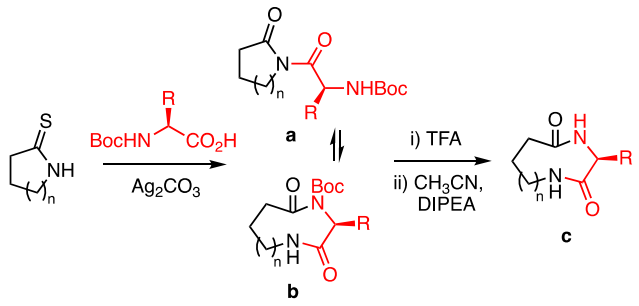
Reaction of the 13-membered laurothiolactam **8** furnished the imide **17a** in good yield after 18 h, with a moderate amount of rearrangement to the ring-expanded product **17b** at this time (Table 2, entry 9). After 48 h, only a minor change was observed, with the **17a** and **17b** formed in excellent overall yield in ~2:1 ratio (Table 2, entry 10).

In all cases, it is apparent that slow interconversion between the initial imide and the ring-expanded adduct is established, with differing ratios dependent on ring size.

We next sought to expand the scope of the appended/inserted amino acid residue beyond the simple Boc-glycine **13**. Accordingly, coupling reactions of Boc-alanine **18** and Boc-phenylalanine **19** were also investigated with 9-membered and 13-membered thiolactams **7** and **8**. Treatment of the 9-membered caprylothiolactam **7** with Boc-alanine **18** in the presence of $Ag_2CO_3$ for 48 h generated the ring expansion product **20b** in 90% yield, with only a trace of the ring open form (Table 3, entry 4). Treatment of **7** with Boc-phenylalanine **19** under the same conditions furnished the ring-expanded product **22b** in 87% yield, along with 9% of imide **22a** (Table 3, entry 5). Treatment of the

larger 13-membered laurothiolactam **8** with Boc-alanine **18** resulted in 58% yield of the imide **21a** and 34% yield of the ring expanded product **21b** (Table 3, entry 7), whereas treatment of with Boc-phenylalanine **19** generated mainly the imide **23a** in 90% yield and the ring expansion product **23b** in 5% yield (Table 3, entry 8).

**Table 3.** Amino acid insertion into thiolactams.[a]



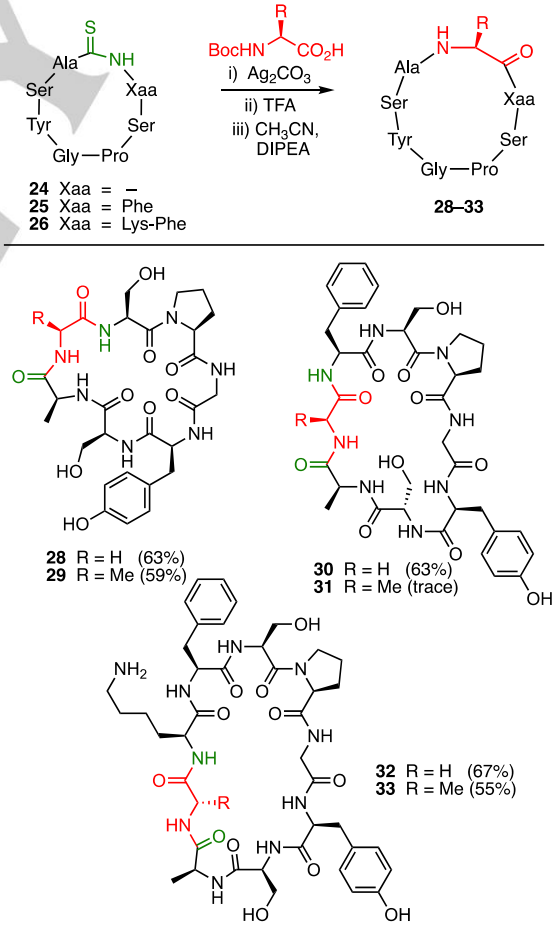

| Entry | n | R | Product | Ratio **a**:**b** | Yield **c** (%) over 2 steps |
|---|---|---|---|---|---|
| 1 | 3 | H | **14** | 1.3:1 | 69 |
| 2 | 4 | H | **15** | 2.0:1 | 54 |
| 3 | 5 | H | **16** | 1:>20 | 89 |
| 4 | 5 | Me | **20** | 1:>20 | 90 |
| 5 | 5 | Bn | **22** | 1:9.7 | 96 |
| 6 | 9 | H | **17** | 2.1:1 | 96 |
| 7 | 9 | Me | **21** | 1.7:1 | 92 |
| 8 | 9 | Bn | **23** | 18:1 | 95 |

[a] Reaction conditions: thiolactam (0.2 mmol), Boc-amino acid **13**, **18** or **19** (0.1 mmol), $Ag_2CO_3$ (0.2 mmol) in $CH_2Cl_2$ (2 mL), rt 48 h; then 1:1 $CH_2Cl_2$:TFA 1 h; then DIPEA (1.0 mmol) in $CH_3CN$ (2 mL), 50 °C, 2 h.

In all cases, coupling of the 9-membered thiolactam **7** with Boc amino acids generates an imide which undergoes acyl migration and ring expansion to afford predominantly the amino acid-inserted macrocycles (i.e. product '**b**') in relatively high yields. In contrast, coupling of the 7-, 8- and 13-membered thiolactams with Boc amino acids generates a mixture of the initial ring open product (product '**a**') and ring expanded product (product 'b'), with the ring open adduct predominating. In order to facilitate the acyl transfer process and complete conversion to the ring expanded product, deprotection of the Boc-protected adducts was performed. Treatment of the mixture of imides **14**–**17a/b** and **20**–**23a/b** with TFA, followed by neutralization with base, effected conversion of the intermediate α-aminoacyl imide (**a**) to the ring-expanded products (**c**). That is, the mixture of imides converge to the desired ring expansion product after Boc-deprotection, in excellent yields (Table 3). Accordingly, the most efficient procedure involves a one-pot, Ag(I)-promoted coupling of Boc-amino acids and thiolactams to generate a mixture of the imides, which is then deprotected with TFA and neutralized with DIPEA to generate the ring expansion products in high yield.

These results are consistent with the related work of Unsworth,[20] with a minor caveat. Unsworth showed that for N-(N'-methylglycinyl) lactams, a 'switch on' point is reached at 8-membered rings at which point the ring expanded form is more stable than the ring-open form, and the acyl migration–insertion process occurs. Our results suggest that for N-glycinyl lactams, possessing a primary amine, the 'switch-on' point is from the 7-membered acylated lactam. These experimental findings are supported by DFT calculations (Table S1).

We next sought to apply this ring expansion methodology to cyclic peptide thioamides. Linear peptide thioamides were prepared[10] and cyclized according to previous protocols.[39] With the cyclic peptide thioamide **24** in hand, Ag(I)-promoted coupling of Boc-glycine was performed at 40 °C in acetonitrile to generate the amino-acid appended adduct. Analysis of this species by RP-HPLC showed two peaks with identical mass, consistent with generation of a mixture of the N-acylated cyclic peptide **27a** and the ring-expanded isomer **27b** (Figure 3). Deprotection of the mixture of **27a/b** with TFA followed by evaporation then dissolution in $CH_3CN/H_2O$/DIPEA furnished cyclic heptapeptide **28** (Scheme 3). Comparison of cyclic peptide **28** with an authentic sample of c(GASPGYA) prepared by standard methods, confirmed the structure of the ring-expanded cyclic peptide (Figure 3).




**Scheme 3.** Ring expansion of cyclic peptide by silver carbonate.

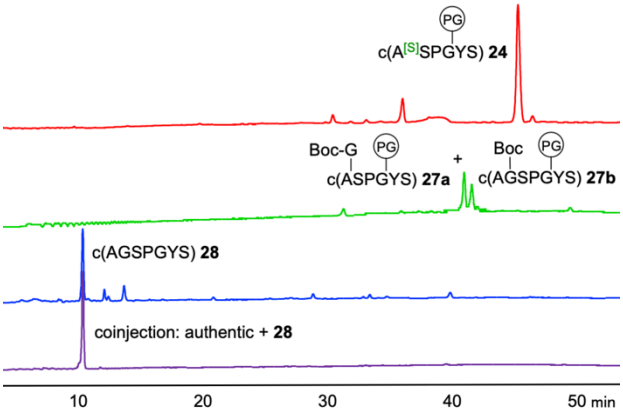



**Figure 3:** Conversion of cyclic thiopeptide **24** to ring expanded product **28** via intermediate **27**.

To explore the scope of this ring expansion methodology variation of the ring size and inserted amino acid were varied. Cyclic hexa-, hepta- and octa-peptides all underwent ring expansion to the corresponding cyclic hepta-, octa- and nona-peptides. Examples of insertion of both glycine and alanine residues were demonstrated, and at different sequence insertion points, typically in good yield (Scheme 3). No evidence for epimerization was observed. In general, insertion of alanine proceeded in slightly lower yield than for glycine, consistent with observations by Unsworth.[17-19] One example proceeded in low yield, with the major product being the cyclic peptide oxoamide. This single example was the insertion of an alanine residue into an Ala–Phe thioamide in cyclic heptapeptide **25** to generate **31**, with a combination of sequence, steric and conformational effects presumably contributing to the low yield in this case.

In conclusion, we have demonstrated a novel Ag(I)-promoted reaction of thiolactams to generate N-(α-aminoacyl)-lactams. A subsequent acyl transfer process facilitates insertion of the α-amino acid to generate a ring-expanded product. Application to cyclic peptides facilitates a site-specific ring expansion process. Ultimately, a single atom substitution (O–S) in a cyclic peptide enables exploitation of the chemoselective reactivity of thioamides to facilitate the site-selective insertion–ring expansion, without necessitating protection of the remaining secondary amide groups.

## Conflict of Interest

The authors declare no conflict of interest.

## Acknowledgements

This work was supported by the Australian Research Council (DP180101804 and DP150100692) and the High Performance Computing Facilities of The University of Melbourne and the National Computational Infrastructure. We acknowledge the support of the Bio21 Molecular Science and Biotechnology Institute MSP and Peptide Technologies facilities. V.T. acknowledges the award of a Norma Hilda Schuster Scholarship.

**Keywords:** ring expansion • thioamides • imides • acyl transfer • ring insertion

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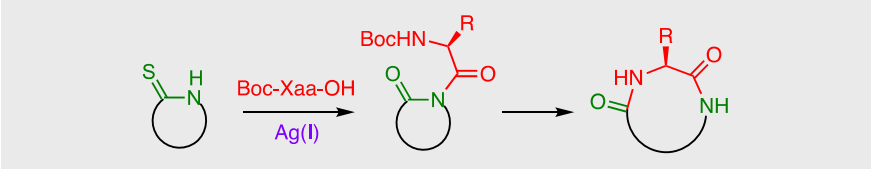


Ag(I)-promoted reaction of thiolactams and amino acids enables an insertion–ring expansion process.

*Jing Shang, Varsha J. Thombare, Carlie L. Charron, Uta Wille and Craig A. Hutton**

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**Ring expansion of thiolactams via imide intermediates: an amino acid insertion strategy**