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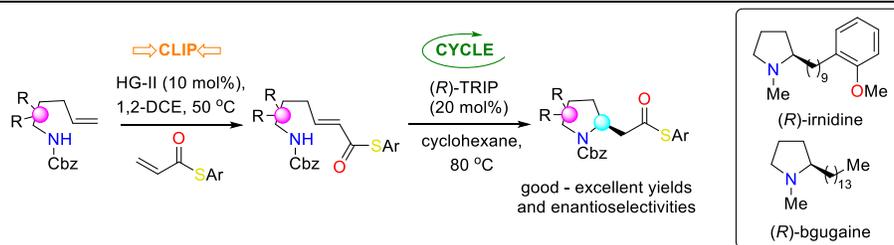
Asymmetric 'Clip-Cycle' Synthesis of Pyrrolidines and Spiropyrrolidines.

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Supporting Information Placeholder



ABSTRACT: The development of an asymmetric 'clip-cycle' synthesis of 2,2- and 3,3-disubstituted pyrrolidines and spiropyrrolidines, which are increasingly important scaffolds in drug discovery programs, is reported. Cbz-protected bis-homoallylic amines were activated by 'clipping' them to thioacrylate *via* an alkene metathesis reaction. Enantioselective intramolecular aza-Michael cyclisation onto the activated alkene, catalyzed by a chiral phosphoric acid, formed a pyrrolidine. The reaction accommodated a range of substitution to form 2,2- and 3,3-disubstituted pyrrolidines and spiropyrrolidines with high enantioselectivities. The importance of the thioester activating group was demonstrated by comparison to ketone and oxoester-containing substrates. DFT studies supported the aza-Michael cyclisation as the rate and stereochemical determining step, and correctly predicted the formation of the major enantiomer. The catalytic asymmetric syntheses of *N*-methyl pyrrolidine alkaloids (*R*)-irnidine and (*R*)-bbugaine, which possess DNA binding and antibacterial properties were achieved using the 'clip-cycle' methodology.

Pyrrolidines appear in nearly 20% of FDA-approved drug molecules which contain a saturated cyclic amine unit,¹ making them one of the most important structural features in modern pharmaceuticals (Figure 1). Recently, spirocyclic amines, including pyrrolidines, have become highly desirable scaffolds²⁻³ as they are conformationally well-defined which allows them to be elaborated along specific vectors. Pyrrolidines are also present in many biologically active natural products.⁴

However, despite this prevalence, the methods available to make them asymmetrically often have drawbacks. A common method is asymmetric lithiation of *N*-Boc pyrrolidine, followed by electrophilic quenching.⁵ The drawbacks of cryogenic temperatures, pyrophoric reagents and the regular use of stoichiometric quantities of chiral diamine are well documented.⁵ The alternative strategies of asymmetric azomethine cycloaddition to olefins,⁶ organocatalytic approaches,⁷ and aza-Michael reactions,⁸ including the asymmetric addition to nitroalkenes⁹ tend to generate products which need to undergo further reactions. An alternative strategy is the *intramolecular* aza-Michael cyclisation, and while there are racemic reactions which generate pyrrolidines in good yields,¹⁰ there are limited examples of asymmetric versions of this reaction. Those which have been reported use chiral auxiliaries on nitrogen,¹¹ or are limited to the formation of specific pyrrolidine substitution patterns.¹² Interest in the synthesis of substituted pyrrolidines and spiropyrrolidines has increased over the last few years due to their recently recognized value in drug discovery projects.^{2,3a,13} However, while new methods to synthesize them have been developed, few are general and asymmetric.¹⁴

A similar variety of substituents were shown to be tolerated at the 2-position of the pyrrolidine¹⁷ (Figure 3). 2,2-Dimethyl substitution (**11a**, Figure 3) resulted in a pyrrolidine product with a 96:4 e.r. Surprisingly, the use of (*R*)-TiPSY resulted in a dramatic decrease in the enantioselectivity of the reaction and the yield (20% yield, 76:24 e.r., **11a**, Figure 3). Running the reaction at 50 °C, did not result in an increase in the enantioselectivity, only in a reduced conversion (34% yield, Figure 3). Changing the solvent to either DCE or toluene only led to a reduction in yield of **11a** (Figure 3).

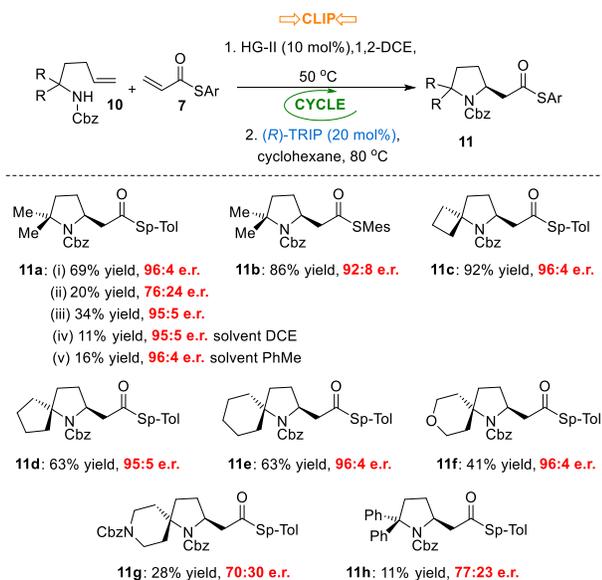


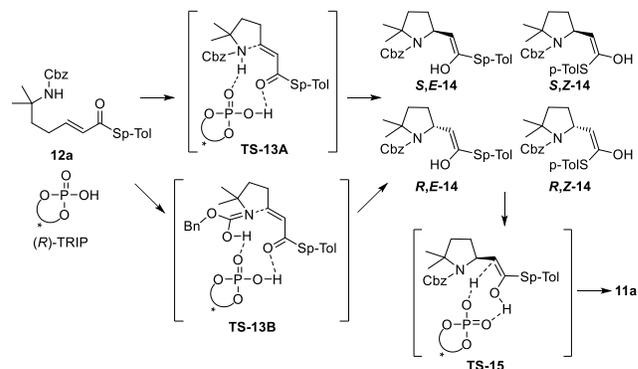
Figure 3. Asymmetric 'Clip-Cycle' Synthesis of 2,2-Disubstituted Pyrrolidines. Yields are reported over two steps. Enantiomeric ratios were determined by chiral stationary phase HPLC. In the case of **11a** (ii) (*R*)-TiPSY (20 mol%) was used as the catalyst. In (iii-v) the reaction was heated to 50 °C. In the case of **11h** the reaction was run for 48 h.

Replacing the *p*-tolyl thioester with a mesityl thioester, also resulted in 92:8 e.r (**11b**, Figure 3). A range of cycloalkyl substituents could be introduced with no detrimental effect on the enantioselectivity of the pyrrolidine product (**11c-f**, Figure 3). However, when 4-*N*-Cbz-piperidyl or 2,2-diphenyl substitution was present the yields and enantioselectivity of the reaction were lower (**11g-h**, Figure 3). This could be due to the increased steric bulk of the diphenyl groups or the additional *N*-Cbz-group interacting with CPA catalyst. Thus, (*R*)-TRIP was still the optimal CPA for the 'clip-cycle' reaction, although the reaction is slightly less tolerant of 2,2-disubstitution than of 3,3-disubstitution.

Intrigued by the high levels of enantioselectivity, the 'clip-cycle' reaction was investigated computationally. Our working mechanistic hypothesis (Scheme 3) was that the carbamate nitrogen in **12a** directly cyclizes on to the α,β -unsaturated thioester, forming the aminoenol **14**, which then tautomerizes to give the pyrrolidine product **11a**. The aminoenol can have either *S* or *R* stereogenic center configuration, and either *E* or *Z* enol geometry depending on whether the thioester adopts an *s-cis* or *s-trans* conformation in **TS-13A**. Investigation of all 4 combinations was necessary to identify the lowest energy

pathway. Both steps could be catalyzed by the CPA. An alternative pathway proceeding *via* an iminol and corresponding cyclization transition state **TS-13B** was also briefly considered, but early model studies found that this pathway is much higher in energy and was not investigated in more detail.

Scheme 3. Mechanistic hypothesis for enantioselective CPA-catalyzed aza-Michael cyclization.



Conformational searches were done on the starting material, intermediates, products and transition-state-like structures. Selected conformers were then reoptimized at DFT level, and free energies calculated (B3LYP¹⁹/6-31G**²⁰/SMD(cyclohexane)²¹//Mo6-2X²²/def2-TZVP²³/SMD(cyclohexane), see SI for further details). Computational results (Figure 4) show that the Brønsted acid acts as a proton shuttle and catalyzes both the cyclization to give the aminoenol **14**, and its subsequent tautomerisation to the thioester **11a**. The cyclization is the rate-limiting and stereochemical-determining step. Computations indicate that the *S,E* pathway is the most favorable, and the next lowest-energy competing pathway is the enantiomeric *R,Z* pathway. The main difference between these competing transition states is the orientation of the thioester α -proton: in the *S,E* TS it is pointing away from the catalyst pocket, while in the *R,Z* TS it is pointing in-wards to allow amide to approach from the other side. This steric clash is presumably the main reason for the difference in the energies. The free energies of the remaining *S,Z* and the *R,E* cyclization transition states were 27.9 kcal/mol and 29.4 kcal/mol, respectively, which is much higher than in the *S,E* and the *R,Z* pathways. Our computational study predicted formation of the (*S*)-product **11a** with 93:7 e.r. which fits well the experimentally observed value of 96:4 e.r.

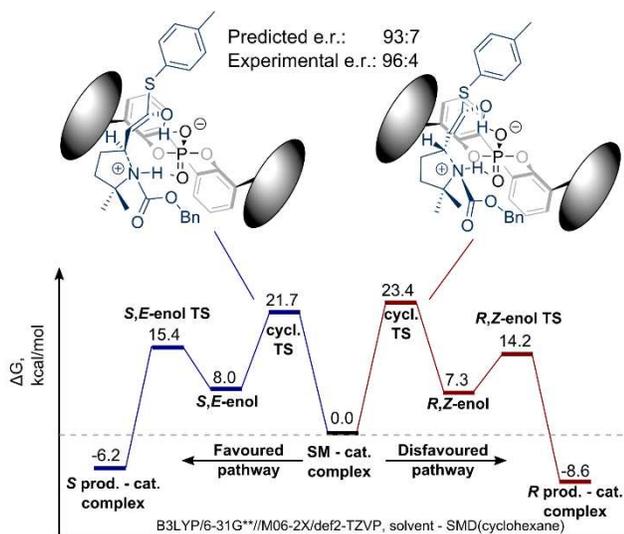
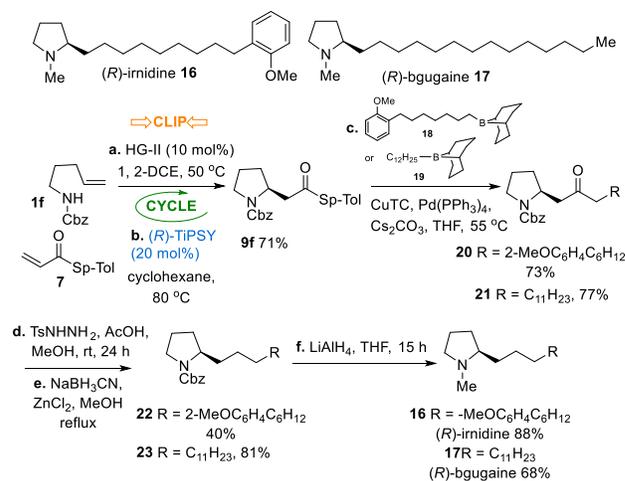


Figure 4. Results from the computational study of CPA catalyzed enantioselective aza-Michael reaction

N-Methyl pyrrolidine-containing alkaloids such as (*R*)-irnidine^{24a} **16** and (*R*)-bgugaine^{24b} **17** have been shown to have a strong binding affinity for DNA,²⁵ and possess antibiotic properties against Gram +ve bacteria,^{24b} (*R*)-bgugaine is also a potent hepatotoxin.²⁶ To date there have been three racemic total syntheses²⁷ and five total syntheses of single enantiomers of these alkaloids,²⁸ where the stereochemistry was either set from the chiral pool or *via* the use of a chiral auxiliary. One report utilized a Sharpless asymmetric dihydroxylation reaction to install the required stereochemistry.^{28f} Clip-cycle pyrrolidine formation enabled the short, catalytic enantioselective total syntheses of these alkaloids (Scheme 4).

The total syntheses of both (*R*)-irnidine and (*R*)-bgugaine were achieved from a common β -homoproline intermediate **9f**. β -Homoproline thioester **9f** was synthesized in 94:6 e.r. and 71% isolated yield over two steps by the 'clip-cycle' reaction using (*R*)-TiPSY. A Liebeskind-Srogl coupling of **9f** with the appropriate alkylborane (**18** or **19**) yielded **20** or **21** in 73% and 77% yields respectively. Wolf-Kischner reduction of **20** and **21** *via* formation of the tosyl hydrazone (88% and 90% yields for the hydrazone formation from **20** and **21** respectively) was followed by reduction with NaBH₃CN and ZnCl₂ to give **22** in 40% yield and **23** in 81% yield over two steps. Finally, LiAlH₄ reduction of the Cbz groups of **22** and **23** delivered the natural products (*R*)-irnidine **16** and (*R*)-bgugaine **17** in 88% and 68% yields in 6 steps from **1f**.

Scheme 4. Total syntheses of (*R*)-irnidine and (*R*)-bgugaine^a



^aReagents and conditions: **a.** Hoveyda-Grubbs II (10 mol%), CuI, DCE, 50 °C, 14 h, 88%; **b.** (*R*)-TiPSY (20 mol%), cyclohexane, 80 °C, 81%; **c.** **18** or **19**, CuTC, Pd(PPh₃)₄ (5 mol%), Cs₂CO₃, THF, 55 °C, 20 h, 73% (**20**) 77% (**21**); **d.** TsNHNH₂, AcOH (cat.), MeOH, 24 h 88% (**20**), 90% (**21**); **e.** NaBH₃CN, ZnCl₂, MeOH, reflux, 16 h, 40% (**22**), 81% (**23**); **f.** LiAlH₄, THF, 15 h, 88% (**16**), 68% (**17**). HG-II = Hoveyda-Grubbs 2nd generation catalyst, CuTC = copper (I) thiophene-2-carboxylate.

In conclusion we have developed a modular and enantioselective Brønsted acid-catalyzed 'clip-cycle' synthesis of 2,2- and 3,3-disubstituted pyrrolidines and spiroyrrolidines, which are key units in drug discovery programs, and we have used this in the catalytic enantioselective synthesis of (*R*)-irnidine and (*R*)-bgugaine in 18% and 33% overall yields respectively. This method compares favorably with other methods for the synthesis of pyrrolidine natural products, including those which utilize aza-Michael reactions as it avoids the need for cryogenic temperatures²⁹ and yields the natural products in only 6 steps. Investigation into substrates with additional double bond substitution and kinetic resolution of racemic substrates are ongoing and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Full experimental procedures and analysis data for all new compounds, overview of the computational methods and results (PDF). Full set of DFT output files with optimized structures, frequencies and high-level single-point energies can be found at <https://doi.org/10.17863/CAM.50976>. Additional reference spectroscopic and reaction data can be found at DOI: 10.15124/a01fe9be-9b9e-43ac-8a21-20a9075784c5

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Notes

The authors declare no competing financial interest.

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