Article | Received 12 August 2026; Revised 16 September 2026; Accepted 23 September 2026; Published 3 November 2026
https://doi.org/10.55092/asymmetry20260007

Isochalcogenourea-catalysed enantioselective synthesis of pyrrolidinone and chromeno-pyrrolidine heterocycles

Sonia Kharb[1,†], Jerson E. Lapetaje[1,†], Kevin Kasten[1], Tengfei Kang[1,2], Claire M. Young[1], Matthew T. Westwood[1], Aidan P. McKay[1], David B. Cordes[1] and Andrew D. Smith[1,*]

[1] EaStCHEM, School of Chemistry, University of St Andrews, St Andrews, UK
[2] Key Laboratory of Applied Surface and Colloid Chemistry of Ministry of Education, School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an, China

† These authors contributed equally to this work.

* Correspondence author; E-mail: ads10@st-andrews.ac.uk.

Highlights:

- An organocatalytic Michael addition using aza-allylic anion equivalents and α,β-unsaturated acyl ammonium species generated from N-acylation of isochalcogenourea catalysts such as BTM, HyperBTM or HyperSe with α,β-unsaturated aryloxide esters is described.
- Hydrolysis of the imine functionality within the Michael addition product enables lactamisation with excellent stereospecificity to access highly enantioenriched pyrrolidinones (γ-lactams).
- Extension of this approach through tuning substrate design allows the synthesis of chromeno-pyrrolidines via a Michael addition/intramolecular Mannich reaction/lactonization sequence.

Abstract: Pyrrolidinone-containing heterocycles are important scaffolds in natural products and highly relevant for the pharmaceutical industry. Although previous reaction processes have addressed the asymmetric synthesis of these heterocycles, the use of readily available, cheap and bench-stable precursors (such as α,β-unsaturated esters) is still of synthetic interest. Herein we present the isochalcogenourea-catalysed chemo- and enantioselective synthesis of pyrrolidinones (γ-lactams) in up to 95% yield, 95:5 dr and 94:6 er via a Michael addition/hydrolysis/lactamisation cascade. The corresponding Michael addition product could be isolated prior to hydrolysis and functionalised to generate a range of ester and amide products in up to 81% yield, > 95:5 dr and 98:2 er. In addition, a switch in chemoselectivity to obtain chromeno-pyrrolidines in up to 58% yield, > 95:5 dr and 99:1 er via a Michael addition/intramolecular Mannich reaction/lactonisation sequence was achieved. Strategic placement of an *ortho*-hydroxy group within the benzophenone imine moiety was used to increase imine electrophilicity via hydrogen bonding and therefore facilitate the intramolecular Mannich reaction.

Keywords: isothiourea; organocatalysis; asymmetry; pyrrolidinone; chromene; Michael addition; Mannich reaction; aryloxide catalyst turnover

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1. Introduction

The pyrrolidinone scaffold constitutes an important heterocycle that commonly serves as a core structural motif within a wide range of natural products and pharmaceutically relevant compounds [1,2]. For example, pyrrolidinone alkaloids such as Amathaspiramides A, C and E [3], as well as Lactacystin [4] have a diverse range of biological activities that include antiviral and antiproliferative activity (Figure 1a). The incorporation of this motif can also lead to enhanced biological activity, as shown by the insertion of an amidopyrrolidone at C(7) within the suberoylanilide hydroxamic acid (SAHA) skeleton **1** that leads to an increase in cytotoxicity (Figure 1a) [5]. The diverse pharmacological activity exhibited by chiral pyrrolidinone derivatives has made their enantioselective synthesis an important objective in modern organic and medicinal chemistry and a variety of strategies have been reported for their synthesis. A widely employed strategy for the construction of these heterocyclic frameworks involves a tandem sequence consisting of a C-C bond forming enantioselective Michael addition of a protected N-containing carbanion equivalent, followed by N-deprotection that triggers intramolecular lactamisation. As representative examples of this approach, an efficient one-pot two-step synthesis of pyrrolidinone derivatives was reported by Zhao and co-workers using squaramide-cinchona alkaloid bifunctional catalyst **2** [6]. Their approach involved initial enantioselective conjugate addition of a nitroalkane to an isatin-derived α-trifluoromethylacrylate, followed by reduction to the corresponding amine, which induces intramolecular lactamisation to give the desired pyrrolidinone compound in high yield and enantiocontrol (up to 98:2 er and 95% yield, Figure 1b). Alternative Michael addition lactamisation processes were demonstrated by Ye and co-workers employing the chiral NHC **3**. Starting from an α,β-unsaturated acid, *in situ* generation of the activated mixed anhydride facilitated formation of the corresponding α,β-unsaturated acyl azolium intermediate that underwent enantioselective C-C bond formation from an α-amino ketone, followed by lactamisation, to give 2,3-disubstituted pyrrolidinones in good yield and high stereoselectivity (Figure 1c, left) [7]. Alternatively, using NHC **3** with an α-chloroaldehyde generated the corresponding azolium enolate intermediate that underwent Michael addition to give a γ-amino-α,β-unsaturated enone. Consecutive lactamisation led to the corresponding 3,4-substituted pyrrolidinone derivatives (Figure 1c, right) [8]. The chromeno-pyrrolidine molecular scaffold is also of considerable interest and can be accessed through a conceptually related cascade process. In this case, *ortho*-hydroxy aldimine pro-nucleophiles are used in an initial conjugate addition to an acceptor, followed by intramolecular Mannich reaction and lactonisation as demonstrated through the use of α-bromo enals using NHC-catalysts (Figure 1d) [9]. A range of alternative acceptor motifs have been used within this area, including α,β-unsaturated azlactones [10,11], alkylidene Meldrum's acid [12], β,γ-unsaturated-α-keto esters [13], cyclopropenones [14], 2*H*-chromen-2-ones [15], β,γ-unsaturated-α-ketophosphonates [16,17] and allenoates [18].

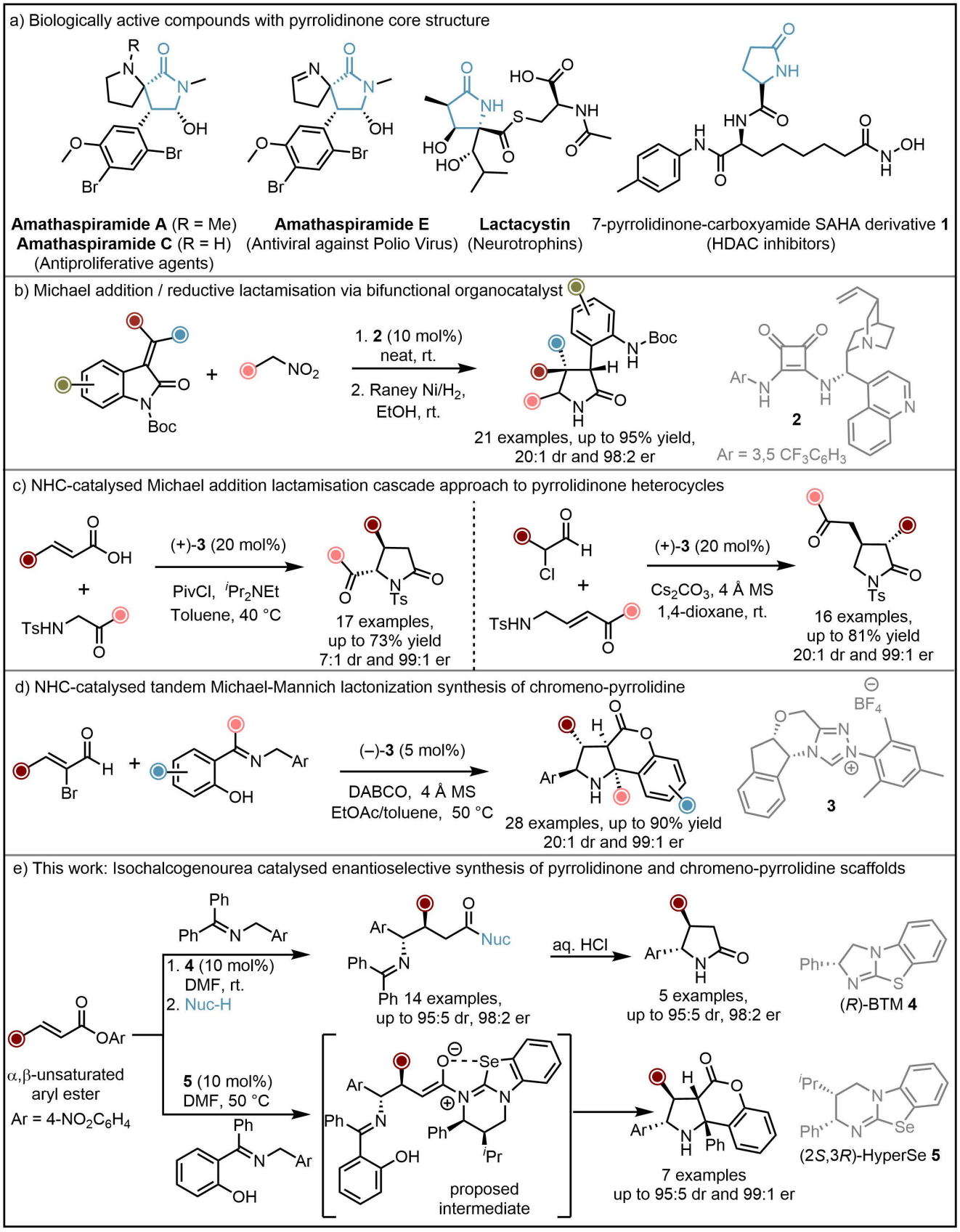


Figure 1. State-of-the-art pyrrolidinone and chromenone synthesis. **(a)** Importance of pyrrolidinone heterocycles; Enantioselective pyrrolidinone heterocycle synthesis with **(b)** bifunctional catalyst and **(c)** NHC catalyst; **(d)** NHC catalyst in the asymmetric synthesis of chromeno-pyrrolidine heterocycles; **(e)** This work.

Isochalcogenoureas have emerged as highly versatile Lewis basic organocatalysts in a wide range of enantioselective transformations [19–30]. They are commonly used to generate chiral α,β-unsaturated acyl ammonium intermediates *in situ*, which have been harnessed in a range of enantioselective Michael addition processes to form C-C [31–38], C-N [39], C-S [40] and C-Se [40] bonds by ourselves and others. In previous work, we demonstrated the enantioselective N-addition of *ortho*-hydroxybenzophenone imines to α,β-unsaturated esters, giving the corresponding β-imino ester products in high yield and enantioselectivity [39]. Essential to the observed reactivity in this system was the *ortho*-hydroxy substituent, playing an essential role in hydrogen bonding to promote the desired reactivity as elegantly previously demonstrated by Alemán and co-workers [41,42]. Building upon these precedents, this manuscript demonstrates the isothiourea **4** catalysed addition of *N*-(*para*-nitrobenzyl)ketimines to *in situ* generated α,β-unsaturated acyl ammonium intermediates derived from α,β-unsaturated esters to generate the corresponding γ-iminoester products. Imine hydrolysis promotes lactamisation to give the desired pyrrolidinone products (Figure 1e, top). Extension of this approach demonstrates that isoselenourea **5** catalysed Michael addition of *ortho*-hydroxy-substituted *N*-(*para*-nitrobenzyl)ketimines to α,β-unsaturated acyl ammonium intermediates, followed sequentially by intramolecular Mannich reaction and lactonisation generates the related chromeno-pyrrolidine motif (Figure 1e, bottom). Although numerous methods are available for the enantioselective synthesis of both pyrrolidinone and chromeno-pyrrolidine derivatives, to the best of our knowledge the use of α,β-unsaturated esters as abundant, cheap and bench-stable starting materials for their synthesis has not been demonstrated previously.

2. Methods

(1) Representative procedure for the generation of Michael addition products

The requisite α,β-unsaturated aryl ester **6** (1.0 equiv.), *para*-nitrophenyl imine **7** (1.5 equiv.), and (*R*)-BTM catalyst **4** (10 mol%) were reacted in anhydrous dimethylformamide (0.1 M) and stirred for 8 hours at room temperature. Piperidine (1.5 equiv.) was added, and the reaction was stirred for 16 hours at room temperature. The mixture was then concentrated *in vacuo* and purified by column chromatography under the conditions specified to afford final product **11**.

(2) Representative procedure for the hydrolysis/lactamisation of γ-iminoesters

The requisite amount of γ-imino substituted amide product **11** (1.0 equiv.) and 10% HCl (5.0 equiv.) were reacted in THF (0.1 M) and stirred for 16 hours at room temperature. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, and washed successively with saturated $NaHCO_3$ and water (× 3). The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and purified by column chromatography under the conditions specified to afford final product **24**.

(3) Representative procedure for the generation of chromeno-pyrrolidines

The requisite α,β-unsaturated ester **6** (1.0 equiv.), *ortho*-hydroxy-substituted *N*-(*para*-nitrobenzyl)ketimine **29** (1.5 equiv.), 8-MeO-HyperSe catalyst **5** (10 mol%) and anhydrous dimethylformamide (0.1 M) were transferred into a flame-dried round-bottom flask. The reaction was stirred for 23 hours at 50 °C. The mixture was concentrated *in vacuo,* and HCl (1.0 M) and THF (0.1 M) were added into the reaction mixture to hydrolyse the remaining starting material and side-product. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, and washed successively with saturated $NaHCO_3$ and water (× 3). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Further purification by column chromatography was performed to afford final product **30**.

3. Results

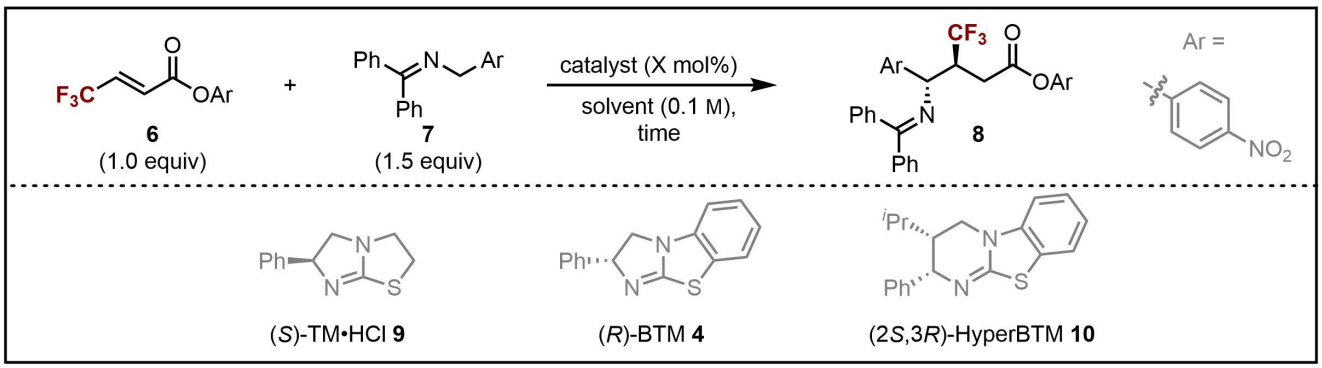
3.1. Enantioselective conjugate addition and cyclisation approach to pyrrolidinones

Initial investigations treated β-CF_3 α,β-unsaturated *para*-nitrophenyl ester **6** with *para*-nitrophenyl imine **7** in the presence of 10 mol% of (*R*)-BTM **4** and 10 mol% triethylamine in acetonitrile for 48 hours (Table 1, Entry 1). This provided the desired γ-iminoester Michael addition product **8** in modest yield but with promising levels of enantio- and diastereocontrol (43% yield, 88:12 er, 79:21 dr). A control reaction in the absence of the isothiourea organocatalyst indicated a competent background process taking place giving the desired product **8** in comparable yield and diastereoselectivity (Entry 2). Exploration of several alternative reaction solvents including CH_2Cl_2 and THF showed decreased levels of both reactivity and enantioselectivity (Entries 3–4), albeit with increased diastereoselectivity. In solvents such as Et_2O, PhMe and EtOAc only trace amounts of product **8** were formed (Entries 5–7). Changing to polar aprotic solvents such as DMA and DMSO showed increased reactivity and diastereoselectivity, albeit with decreased enantioselectivity (Entries 8–9). The use of DMF provided the γ-iminoester **8** in high yield and diastereoselectivity with promising enantioselectivity (> 95:5 dr, 86:14 er, Entry 10). Omission of triethylamine suppressed the base-promoted background reaction and hence led to an increase in the observed product enantioselectivity, with **8** obtained in 81% yield (56% Isolated yield), > 95:5 dr and 95:5 er (Entry 11). The alternative isothiourea catalysts TM·HCl **9** and (2*S*,3*R*)-HyperBTM **10** were also trialled but led to reduced product yield and enantioselectivity (Entries 12 and 13). Decreasing the catalyst loading from 10 mol% to 5 mol% led to significantly reduced product yield whilst maintaining enantioselectivity (Entry 14).

With optimal conditions developed (Table 1, Entry 11), the generality of the developed methodology was probed through variation of both the aryl ester and imine components. The marked difference between the yield determined by ^{1}H NMR analysis of the crude reaction mixture and the isolated yield of the product **8** is suspected to be due to ester hydrolysis upon chromatographic purification on silica. Consequently, a post-catalysis nucleophilic addition with either a primary or secondary amine, or an alcohol, was performed to generate a stable product. After completion of the reaction using the developed conditions, piperidine was added as a nucleophile providing the corresponding amide product **11** in 81% yield, 95:5 dr and 95:5 er (Figure 2). The relative and absolute configuration within (3*S*,4*S*)-**11** was identified unambiguously by single crystal X-ray diffraction, with all subsequent derivatives assigned by analogy. Frustratingly, the enantioselectivity of product **11** fluctuated markedly (ranging from 85:15 to 95:5 er) upon chromatographic purification on silica. Building upon previous observations, this was proposed to be due to the phenomenon of self-disproportionation of enantiomers (SDE) [43,44], with the er of a given sample not necessarily representative of the entire reaction mixture. Although the scope of the developed catalytic process is demonstrated below, control over fluctuation in product er proved difficult in certain cases. Expansion of this approach to alternative nucleophilic primary and secondary amines was tested, with morpholine and pyrrolidine giving the corresponding amide products **12** and **13** in high yields and stereocontrol (both > 95:5 dr, Figure 2). Although high enantioselectivity was observed, the er of morpholinone variant **12** varied from 88:12 er to 96:4 er. A benzylamine nucleophilic quench gave the corresponding benzyl amide **14** in 64% yield with high stereoselectivity (> 95:5 dr, 94:6 er), while diethylamine gave amide **15** in 70% yield (95:5 dr, 92:8 er). Transesterification of the *para*-nitrophenyl ester **8** with methanol and benzyl alcohol promoted by a catalytic quantity of

DMAP gave the ester products **16** (> 95:5 dr, 98:2 er) and **17** (> 95:5 dr, 92:8 er), respectively. Application of this method to a small range of electron-deficient α,β-unsaturated aryl esters using *N*-(*para*-nitrophenyl)benzophenone imine **7** was explored (Figure 2). With a β-CF_2H substituent, product **18** was obtained in poor 28% yield but good stereoselectivity (89:11 dr, 92:8 er). The incorporation of alternative perhalogenated substituents gave β-CF_2Cl **19** and β-CF_2Br **20** in moderate yield and high diastereoselectivity (> 95:5 dr) but with reduced enantiocontrol (85:15 er and 89:11 er, respectively). The use of β-carbonyl-based electron-withdrawing groups was next investigated. Product **21** bearing a β-CO_2Et substituent was obtained as a single regioisomer, in good yield (75%) and high diastereoselectivity (89:11 dr), although again fluctuation in product er was observed (from 78:22 er to 92:8 er). β-Dibenzyl amide product **22** was obtained in high stereoselectivity (> 95:5 dr, 97:3 er) but only 20% yield, whereas a β-CO_2Ph ketone substituent provided the corresponding γ-iminoester **23** in modest yield and stereoselectivity.

Table 1. Reaction optimisation for the Michael addition protocol.



Entry	Solvent	Catalyst (mol%)	Base (10 mol%)	Time	Yield (%) [a]	dr [b]	er [c]
1	MeCN	BTM **4** (10%)	Et_3N	48	(43)	79:21	88:12
2	MeCN	-	Et_3N	48	(40)	78:22	N/A
3	CH_2Cl_2	BTM **4** (10%)	Et_3N	48	(15)	94:6	80:20
4	THF	BTM **4** (10%)	Et_3N	48	(12)	86:14	80:20
5	Et_2O	BTM **4** (10%)	Et_3N	48	Trace	-	-
6	PhMe	BTM **4** (10%)	Et_3N	48	Trace	-	-
7	EtOAc	BTM **4** (10%)	Et_3N	48	Trace	-	-
8	DMA	BTM **4** (10%)	Et_3N	48	(86)	> 95:5	67:33
9	DMSO	BTM **4** (10%)	Et_3N	48	(56)	> 95:5	61:39
10	DMF	BTM **4** (10%)	Et_3N	48	(82)	> 95:5	86:14
11	DMF	BTM **4** (10%)	-	8	56 (81)	> 95:5	95:5
12	DMF	TM·HCl **9** (10%)	-	8	(71)	> 95:5	21:79
13	DMF	HyperBTM **10** (10%)	-	8	(67)	> 95:5	92:8
14	DMF	BTM **4** (5%)	-	8	(35)	> 95:5	95:5

Reaction carried out at 0.1 mmol scale at room temperature; [a] Yield given in parentheses was obtained by ^1H NMR analysis of the crude reaction mixture with 1,3,5-trimethoxybenzene as internal standard, yields not in parentheses are isolated yields; [b] determined by ^1H and $^{19}F\{^1H\}$ NMR analysis of the crude reaction mixture; [c] determined by HPLC analysis on a chiral stationary phase.

Further work sought to showcase the synthetic utility of the enantioenriched γ-iminoesters generated using this methodology to give the corresponding pyrrolidinone (γ-lactam) products. Treatment of a range of γ-iminoester products of known er with an excess of aqueous HCl was used to initially promote hydrolysis of the imine functionality to generate the corresponding amine that underwent concomitant intramolecular

cyclisation to the corresponding pyrrolidinone. This strategy proceeded smoothly to generate pyrrolidinones **24**–**28** in excellent yield and without any erosion of stereointegrity compared to the corresponding γ-iminoester starting material (Figure 3a). The relative and absolute configuration within product **24** was confirmed by single crystal X-ray diffraction. To ensure the scalability, the catalytic process was performed on a 4 mmol scale using the β-CF_3 α,β-unsaturated aryl ester **6**, giving pyrrolidinone **24** in comparable yield and stereoselectivity (81% yield, > 95:5 dr, 94:6 er). To further showcase the potential of this method, a one-pot enantioselective Michael addition/hydrolysis and cyclisation cascade sequence was also devised, where the addition of aqueous HCl into the post catalysis reaction flask and subsequent work-up gave pyrrolidinone **24** directly in 80% yield and high stereoselectivity (> 95:5 dr, 94:6 er, Figure 3b).

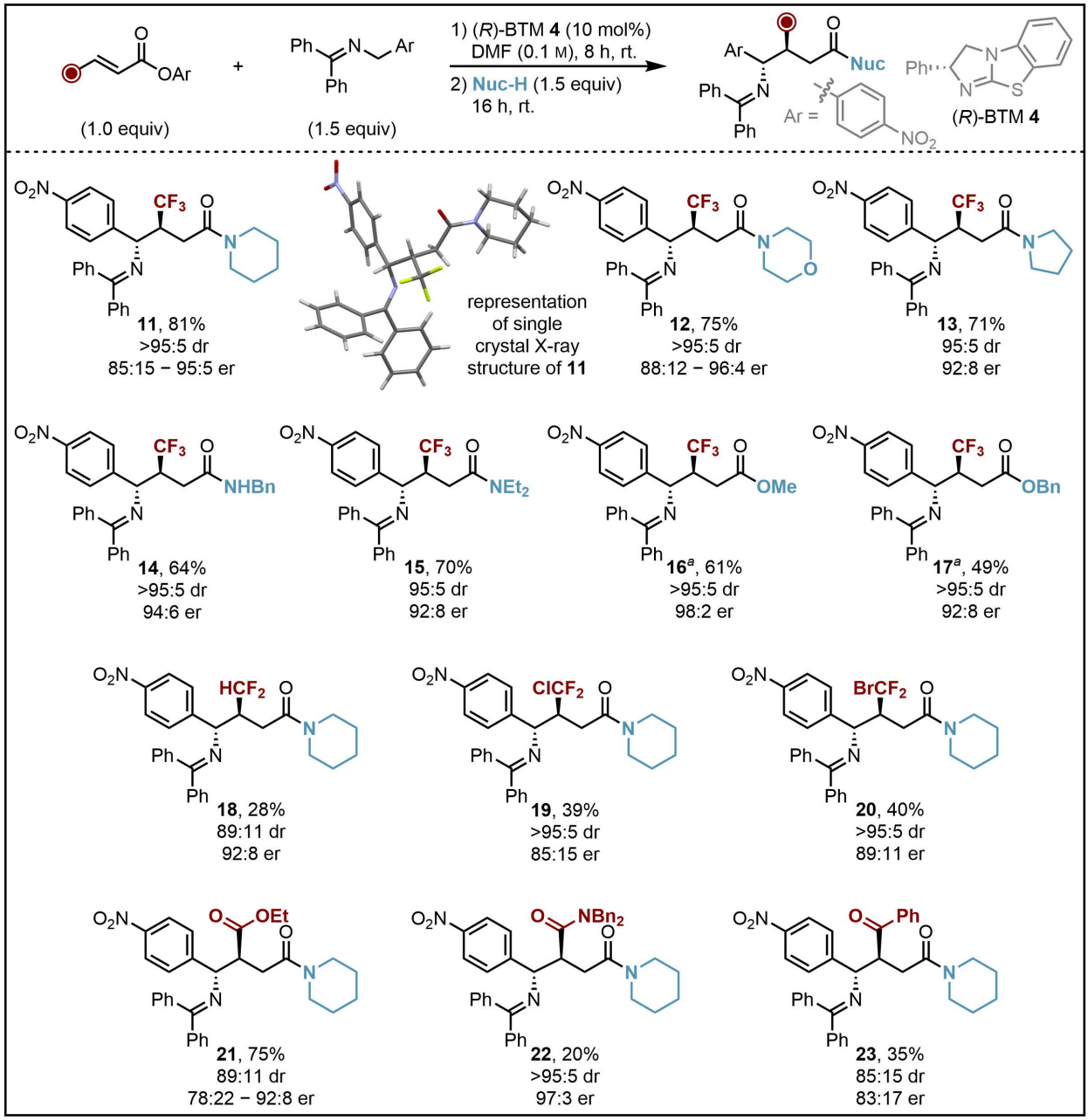


Figure 2. Reaction scope of the Michael addition; Reaction carried out at 0.1 mmol scale; All yields are isolated product yields; dr determined by ^{1}H and $^{19}F\{^{1}H\}$ NMR analysis of the crude reaction mixture; er determined by HPLC analysis on a chiral stationary phase; [a] derivatisation in step (ii) used DMAP (20 mol%) as catalyst.

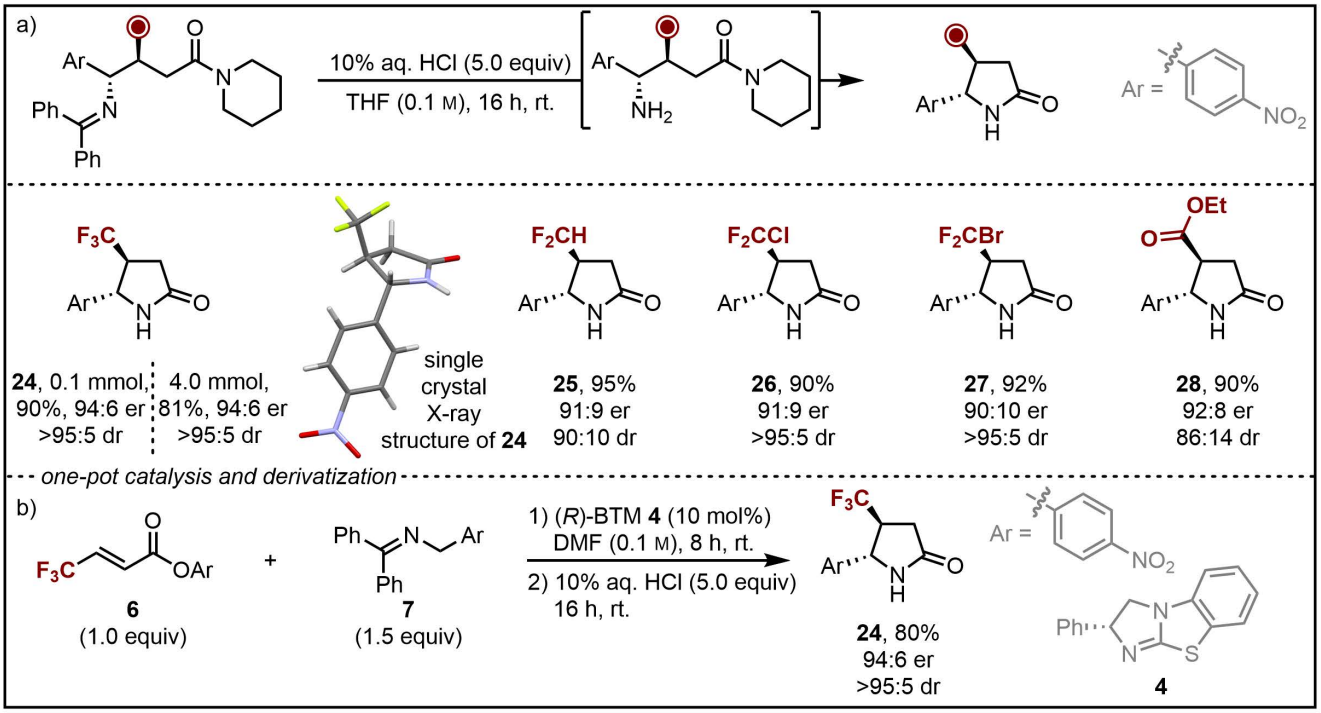
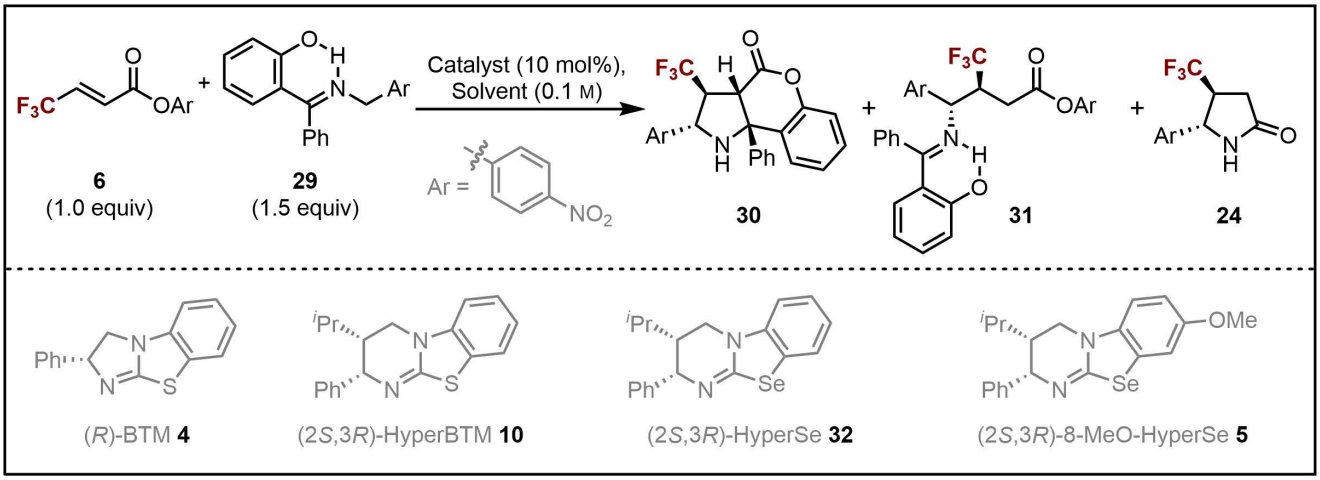


Figure 3. Reaction scope of the Michael addition/hydrolysis/lactamisation cascade. **(a)** Hydrolysis and cyclisation of the Michael addition product. Reaction carried out at 0.1 mmol scale; all yields are isolated product yields; dr determined by ^{1}H and ^{19}F{^{1}H} NMR analysis of the crude reaction mixture; er determined by HPLC analysis on a chiral stationary phase; **(b)** One-pot catalysis and *in situ* hydrolysis/cyclization.

3.2. Enantioselective conjugate addition/Mannich/lactonisation cascade

With these results in hand, extension of this protocol to allow the synthesis of chromeno-pyrrolidine heterocycles was considered. Upon use of *ortho*-hydroxy-substituted benzophenone imine **29** under the previously optimised reaction conditions, an alternative fused ring product **30** was formed (37% yield, > 95:5 dr, > 99:1 er) along with Michael addition product **31** (11% yield) and pyrrolidinone **24** (26% yield) (Table 2, Entry 1). Further optimisation sought to increase the yield of **30** by promoting the conversion of Michael addition product **31** and avoiding hydrolysis to form pyrrolidone **24**. A range of polar and apolar solvents was trialled (for full details see SI) that indicated a decrease in solvent polarity resulted in complete loss of reactivity (Entries 2–4). In alternative highly polar solvents DMSO and DMA, a similar yield of **30** with high stereoselectivity was observed (Entries 5 and 6). Using the alternative isothiourea catalyst HyperBTM **10** resulted in a diminished yield of 16% (Table 2, Entry 7), but pleasingly, employing the isoselenourea variant HyperSe **32** increased the yield of **30** to 51% while maintaining high product diastereo- and enantioselectivity (Table 2, Entry 8). Further improvement was observed using the 8-MeO-HyperSe catalyst **5**, giving **30** in 68% yield at room temperature (Entry 9), while increasing the reaction temperature to 50 °C gave chromeno-pyrrolidine **30** in 75% yield (50% isolated yield) with excellent stereoselectivity (Entry 10). The relative configuration within **30** was determined by NOE analysis (see SI for further information), with the absolute configuration established based upon the known facial selectivity upon Michael addition using isochalcogenourea catalyst **5** [45].

Table 2. Reaction optimisation for the Michael addition/Mannich/lactonisation protocol.



Entry	Solvent	Catalyst	30 NMR Yield (%) [a]	31 NMR Yield (%) [a]	24 NMR Yield (%) [a]	30 er [b]
1	DMF	BTM **4**	(37)	(11)	(26)	99:1
2	THF	BTM **4**	-	-	-	-
3	CH_2Cl_2	BTM **4**	-	-	-	-
4	Toluene	BTM **4**	-	-	-	-
5	DMSO	BTM **4**	(29)	(24)	(5)	98:2
6	DMA	BTM **4**	(39)	(29)	(9)	97:3
7	DMF	HyperBTM **10**	(16)	(19)	(14)	97:3
8	DMF	HyperSe **32**	(51)	(13)	(6)	99:1
9	DMF	8-MeO-HyperSe **5**	(68)	(17)	-	99:1
10[c]	DMF	8-MeO-HyperSe **5**	50 (75)	(8)	(8)	99:1

Reaction carried out at 0.2 mmol scale with ester (1.0 equiv.) and imine (1.5 equiv.) at room temperature for 23 hours under N_2 atmosphere; isolated yield is given without parentheses; [a] Yields given in parentheses were obtained by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethoxybenzene as internal standard, yields not in parentheses are isolated yields; [b] determined by HPLC analysis on a chiral stationary phase; [c] reaction at 50 °C; dr always > 95:5.

The developed conditions were next employed to elaborate the scope of the reaction for the synthesis of chromeno-pyrrolidine derivatives (Figure 4). Notably, throughout the development of this reaction, a marked difference in crude product yield (with respect to an internal standard as identified by ^{1}H NMR of the crude reaction mixture) and isolated yield was observed. This significant mass loss during purification is attributed to the polar nature of the product as well as the requirement for multiple chromatographic purifications to attain acceptable product purity. Variation of the β-substituent within the α,β-unsaturated ester component was initially considered, with the β-CHF_2 ester substituent giving the corresponding product **33** in 21% yield (95:5 dr, 97:3 er), while a similar observation was made using the perhalogenated CF_2Cl substituent, giving **34** in 30% yield, although with excellent stereoselectivity (>95:5 dr, 99:1 er). The incorporation of a diethyl amide at β-position was well-tolerated, giving the respective product **35** in 58% yield (>95:5 dr, 97:3 er). An ethyl ester group at the β-position within the α,β-unsaturated ester was also trialled with both (*E*)- and (*Z*)-diastereoisomers as a starting material. The same preferred stereoisomer of product **36** was observed in each case, with product **36** generated in 40% yield (95:5 dr, 94:6 er) from the (*E*)-α,β-unsaturated ester, whereas using the (*Z*)-α,β-unsaturated ester, **36** was isolated in 17% yield with reduced stereoselectivity (95:5 dr, 78:22 er). These results are consistent with the isomerisation of (*Z*)-α,β-unsaturated ester to the thermodynamically more stable

(*E*)-α,β-unsaturated ester during the course of the reaction, presumably via reversible Michael addition of the catalyst or aryloxide to the α,β-unsaturated acyl ammonium intermediate [33]. Although a series of substituted *ortho*-hydroxy-substituted ketimines were synthesised and trialled in this process, satisfactory results were only observed with the incorporation of a methyl group at the C(5') position within the *ortho*-hydroxy ketimine scope. Using α,β-unsaturated esters containing β-ethyl ester and β-CF_3 substituents the corresponding products **37** (32% yield, >95:5 dr and 94:6 er) and **38** (17% yield, 87:13 dr and 99:1 er) were isolated.

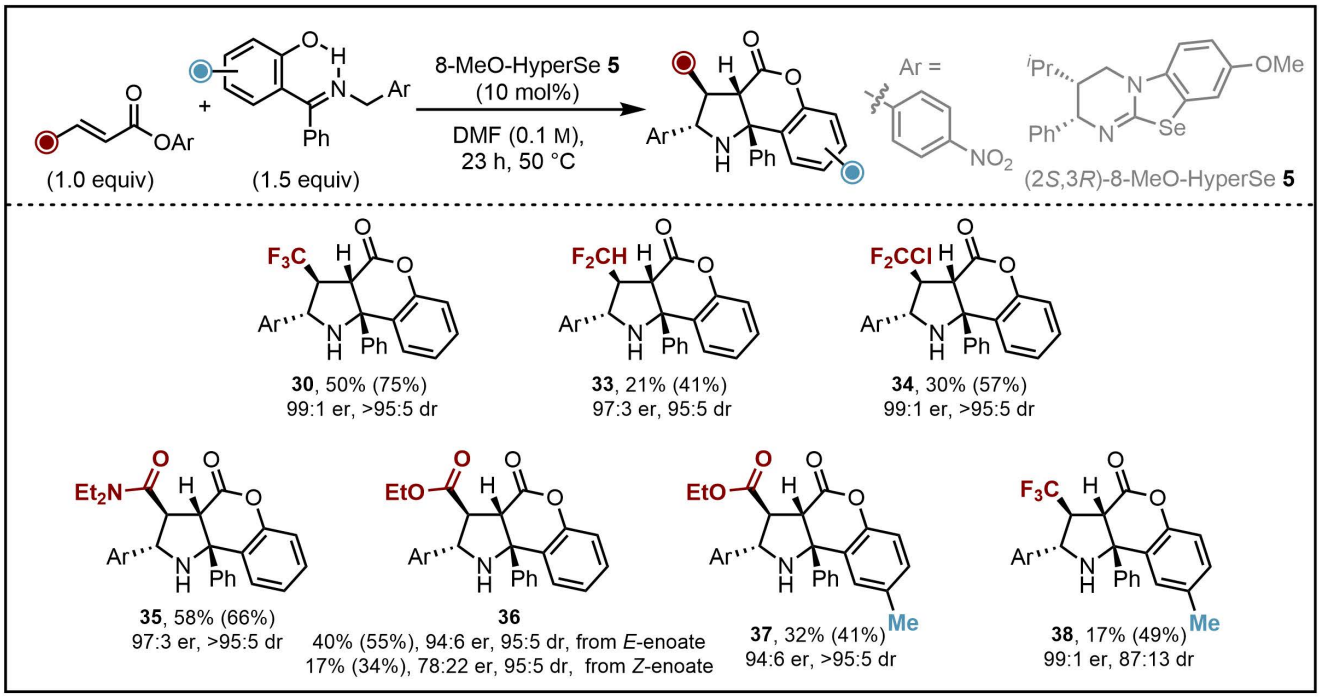


Figure 4. Scope for the Michael addition/Mannich/lactonisation cascade; Reaction carried out at 0.2 mmol scale; Yields given in parentheses were obtained by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethoxybenzene as internal standard, yields not in parentheses are isolated yields; dr determined by ^{1}H and ^{19}F{^{1}H} NMR analysis of the crude reaction mixture; er determined by HPLC analysis on a chiral stationary phase.

On the basis of previous mechanistic studies, catalytic cycles for the observed processes are proposed (Figure 5). A common first step constitutes reversible N-acylation of the nucleophilic isochalcogenourea organocatalyst with α,β-unsaturated aryl ester **6**. This provides the α,β-unsaturated acyl ammonium ion pair **39**. Addition of the aza-allylic anion derived from **7** or **29** to the α,β-unsaturated acyl ammonium intermediate **39** provides the corresponding C(1)-ammonium enolate species **40**. From here, the reaction pathway depends upon the presence of an *ortho*-hydroxy substituent on the pronucleophile. When the substituent is absent, such as in the pronucleophile **7**, and isothiourea (*R*)-BTM **4** is used, then preferential protonation of **40** gives the acyl ammonium intermediate **41**. Subsequent catalyst turnover is promoted by nucleophilic attack of the aryloxide anion, leading to the γ-iminoester product **8**. The observed stereochemical outcome can be rationalised by the α,β-unsaturated acyl ammonium intermediate **39** adopting an s-*cis* conformation with a conformational lock provided by intramolecular 1,5-O•••S chalcogen bonding interaction (highlighted in orange) between the catalyst and the carbonyl of the acyl group [29]. The approach of the aza-allyl anion nucleophile occurs *anti* to the

pseudoaxial phenyl stereodirecting group. An alternative pathway is accessible when an *ortho*-hydroxyl group is present within the benzophenoneimine moiety. The increased electrophilicity of the imine (activated via hydrogen bonding) enables intramolecular enolate attack (Mannich reaction) to give cyclised intermediate **42**, which is prone to undergo intramolecular catalyst turnover from the attack of internally generated aryloxide leading to chromeno-pyrrolidine **30**.

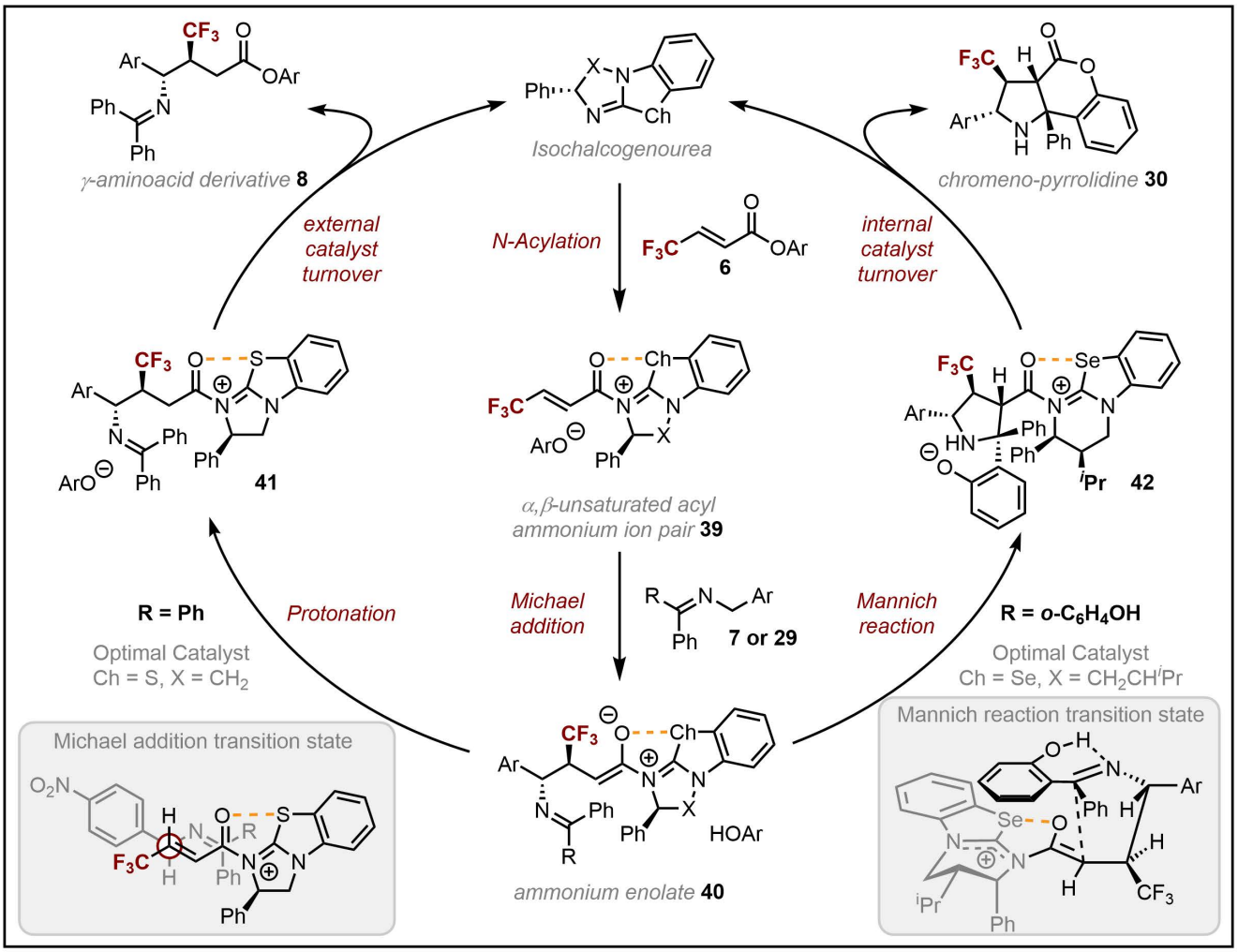


Figure 5. Proposed reaction mechanism.

4. Conclusion

The synthesis of γ-iminoesters (γ-amino acid derivatives), γ-lactams (pyrrolidinones) and chromeno-pyrrolidines from cheap and readily available α,β-unsaturated aryloxide ester and N-benzyl benzophenone imines has been demonstrated. The chemoselectivity between γ-iminoesters and chromeno-pyrrolidines can be controlled by choice of catalyst and the presence of a strategically placed *ortho*-hydroxy group within the benzophenone imine moiety. Yield and enantioselectivity varied due to the high polarity and instability of chromeno-pyrrolidines and γ-iminoesters, which was circumvented in the latter case by *in situ* hydrolysis of the imine to give the pyrrolidinone (γ-lactam) products. Nonetheless, high stereocontrol was achieved throughout making this method an attractive alternative for the synthesis of pyrrolidine-containing heterocyclic systems.

Data availability statement

A supplementary information file is provided containing detailed procedures and compound characterization data and can be downloaded from the publisher's webpage free of charge. The data underpinning this manuscript are available from the University of St Andrews Research Portal, Pure ID: 337669226, "Isochalcogenourea-catalysed enantioselective synthesis of pyrrolidinone and chromeno-pyrrolidine heterocycles'' https://doi.org/10.17630/dfd8cb75-f783-43b8-9487-03e72301ec75. CCDC 2574454-2574455 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Declaration of generative AI and AI-assisted technologies

The authors did not use generative AI or AI-assisted technologies in the writing of this manuscript. The authors take full responsibility for the content of the manuscript.

Acknowledgments

We acknowledge the University of St Andrews (PhD studentship to SK), the DOST-SEI and DOST-Foreign Graduate Scholarship Program of the Philippines for a PhD scholarship (JEL) and the Royal Society for a Newton Fellowship (TK). The research leading to these results has received funding from the EPSRC: Programme Grant "Boron: Beyond the Reagent" (EP/W007517/1, ADS and KK); (EP/T023643/1; KK, TK) and (EP/S019359/1; CMY). We acknowledge support from Dr Tomas Lebl and Dr Siobhan Smith of the St Andrews solution state NMR facility (EP/X034747/1) and Caroline Horsburgh for help with the St Andrews mass spectrometry facility (EP/X034747/1). DBC and APM acknowledge support from EPSRC (UKRI381) and the University of St Andrews Strategic Equipment Fund for funding the single crystal XRD facilities at the University of St Andrews.

Authors' contribution

Conceptualization, A.D.S.; methodology, S.K. and J.E.L.; formal analysis, S.K., J.E.L. and K.K. (NMR and experimental data), A.P.M. and D.B.C. (X-Ray structures); data curation, S.K. and J.E.L.; writing—original draft preparation, J.E.L., M.T.W. and S.K.; writing—review and editing, S.K., K.K. and A.D.S.; supervision, K.K., T.K., C.M.Y. and A.D.S.; funding acquisition, A.D.S. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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