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Anhydrides as α,β-unsaturated acyl ammonium precursors: isothiourea-promoted catalytic asymmetric annulation processes†

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The asymmetric annulation of a range of α,β-unsaturated acyl ammonium intermediates, formed from isothiourea HBTM 2.1 and anhydrides with either 1,3-dicarbonyls, β-ketoesters or azaaryl ketones gives either functionalised esters (upon ring opening), dihydropyranones or dihydropyridones in good yields (up to 93%) and high enantioselectivity (up to 97% ee).

Introduction and background

Asymmetric organocatalysis has developed tremendously as a synthetic strategy within the last decade and a range of methodologies and catalysts have emerged that provide functionalised products with high levels of stereocontrol.[1] Ideally a given organocatalyst architecture should be able to participate in a range of reaction processes and display diverse modes of reactivity, while showing good catalytic efficiency and delivering products with high levels of enantioselectivity. Within this area, isothioureas,[2] initially employed by Birman and Okamoto as efficient *O*-acyl transfer reagents,[3] have been utilised in a range of kinetic resolution,[4] asymmetric desymmetrisation,[5] *C*-acylation and *C*-carboxylation processes,[6] as well as *O*-silylation reactions.[7] Recent advances have showcased the utility of isothioureas to generate ammonium enolates[8] from carboxylic acids and their applications in aldol-[9] and Michael-lactonisation processes (Fig. 1A).[10]

Building upon these precedents, this work demonstrates the previously unexplored ability of isothioureas to generate asymmetry by promoting the addition of a range of nucleophiles to a stereodefined α,β-unsaturated acyl ammonium species (Fig. 1B). While Peters and Ye have invoked α,β-unsaturated acyl ammoniums as precursors to dienolate formation,[11] to the best of our knowledge there are currently no processes that form C–C bonds directly *via* such intermediates. Related work in the literature has shown that NHCs[12] can catalytically generate α,β-unsaturated acyl azolium intermediates through an internal redox process from alkynals,[13] from enals using a stoichiometric oxidant,[14] directly from α,β-unsaturated acyl fluorides or enol esters,[15] or alternatively from α-bromoenones.[16] The oxidative approach from enals has been applied to a range of asymmetric C–C bond-forming reactions including aza-Claisen,[17] Coates-Claisen,[18] cyclopropanation[19] and Michael addition processes.[20] Given the recognised difficulties in accessing a wide variety of ynals and enals for such NHC-catalysed approaches and limitations associated with the scope and generality of such processes,[21] we envisaged a direct strategy to generate an α,β-unsaturated acyl ammonium species from readily available α,β-unsaturated carboxylic acids or their anhydrides. Described herein are our results concerning isothiourea-promoted asymmetric addition of 1,3-diketones, β-ketoesters and azaaryl ketones to α,β-unsaturated acyl ammonium intermediates for the preparation of a range of functionalised esters, stereodefined dihydropyranones and dihydropyridones in highly enantioenriched form (up to 97% ee).

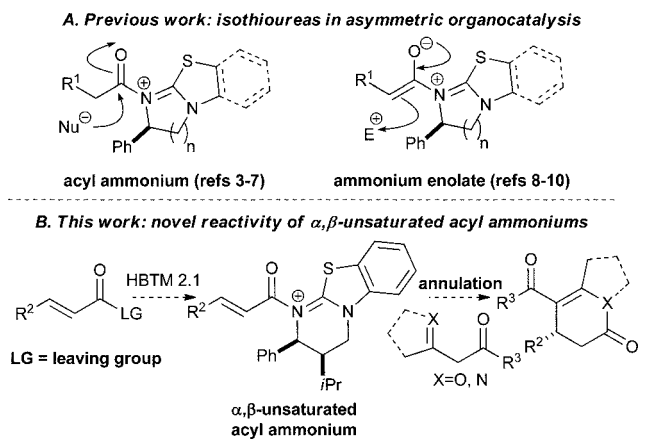

Fig. 1 Proposed access to enantioenriched annulation products *via* an unexplored α,β-unsaturated acyl ammonium species.

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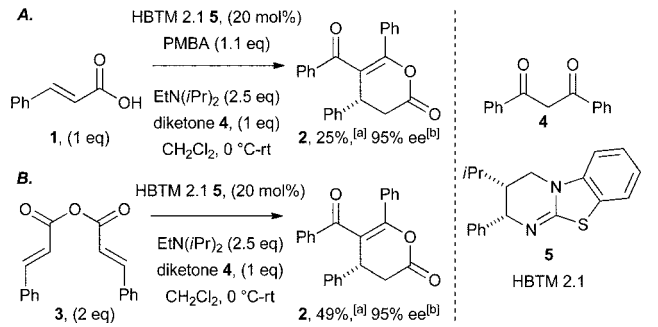
Proof of concept and reaction optimisation: annulations using diketone nucleophiles

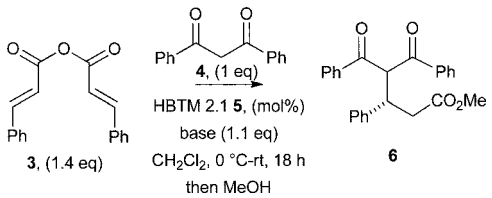
Initial investigations focused upon generation of an α,β-unsaturated acyl ammonium directly from cinnamic acid **1** (Scheme 1A), *via in situ* activation using 4-methoxybenzoic anhydride (PMBA) and isothiourea HBTM 2.1 **5** (20 mol%).[22] Employing diketone **4** as the nucleophile provided dihydropyranone **2** in modest 25% isolated yield, albeit with an encouraging 95% ee. Cinnamic anhydride **3** was next evaluated as an alternative acyl ammonium precursor,[23] giving dihydropyranone **2** in improved 49% yield and 95% ee (Scheme 1B). These initial findings served as a benchmark for further optimisation with the aim to lower catalyst loadings and improve isolated yields.[24]



Scheme 1 Initial proof of concept studies. [a]Isolated yield of **2**; [b]determined by HPLC analysis.

Further studies showed that *in situ* ring opening of dihydropyranone **2** with MeOH led to consistently higher isolated yields of the functionalised ester product **6** (Table 1). Variation of the base showed that $EtN(iPr)_2$, DBU or PS-BEMP (polymer-supported 2-*t*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine) could be used in this process, although DBU gave **6** with reduced enantioselectivity (entry 5).[25] The use of PS-BEMP proved optimal, allowing the catalyst loading of HBTM 2.1 **5** to be reduced to 1 mol% without compromising product enantioselectivity, albeit with reduced product yields (entry 11). Performing the reaction in THF led to a reduced yield (entries 4 and 9). While catalytic asymmetric Michael additions to nitro-olefins and enones are well documented,[26] this strategy formally allows the asymmetric Michael addition of diketones to α,β-unsaturated carboxylic acid derivatives for which there is only limited precedent.[27]

Table 1 Optimisation studies



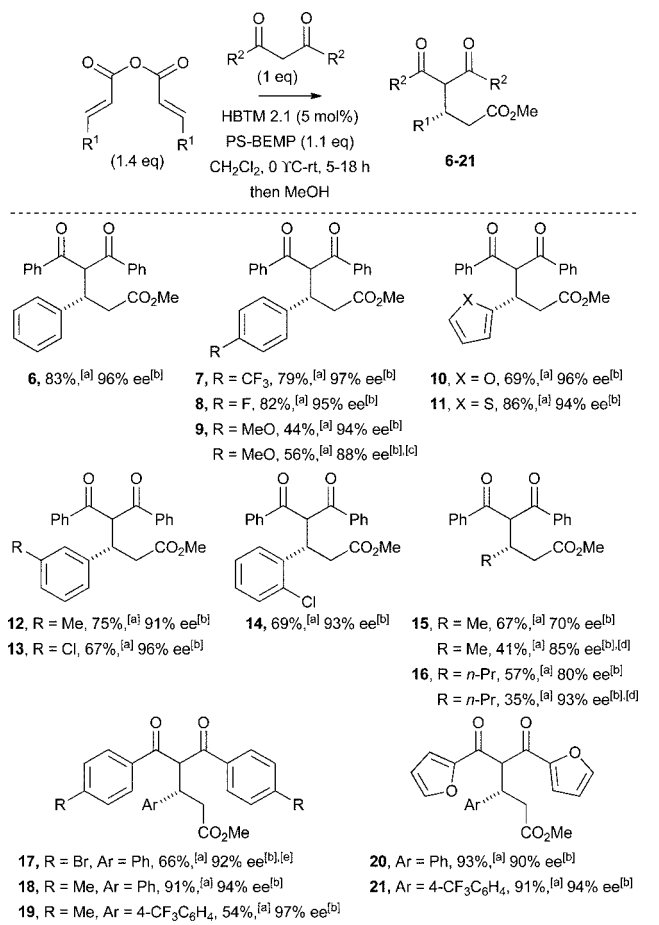
Entry	HBTM 2.1 (mol%)	Base	Yield[a]	ee[b] (%)
1	20	$EtN(iPr)_2$	77	96
2	10	$EtN(iPr)_2$	70	95
3	5	$EtN(iPr)_2$	62[c]	—
4[d]	5	$EtN(iPr)_2$	45	99
5	20	DBU	86	73
6	20	PS-BEMP	85	95
7	10	PS-BEMP	82	95
8	5	PS-BEMP	83	96
9[d]	5	PS-BEMP	50	83
10	2.5	PS-BEMP	69	93
11	1	PS-BEMP	62	93

[a] Isolated yield of **6**. [b] Determined by HPLC analysis. [c] Conversion determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [d] Reaction conducted in THF.

Reaction scope and generality

The generality of this process was next probed, initially through variation of the α,β-unsaturated anhydride component (Table 2). Using HBTM 2.1 **5** (5 mol%) and a number of symmetrical diketones, this protocol tolerates a range of 2-, 3-, and 4-substituted β-aryl groups containing either electron-withdrawing or electron-donating groups, as well as heteroaryl

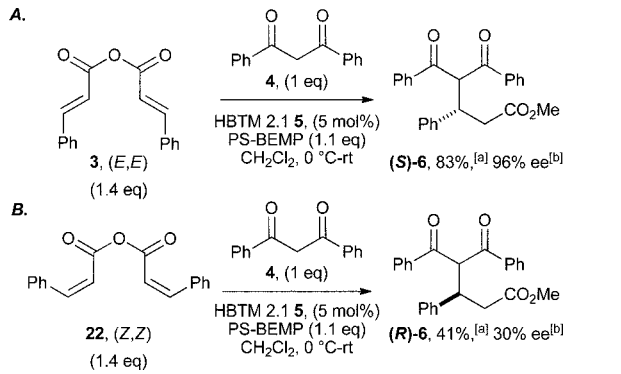
Table 2 Substrate scope



[a] Isolated yield of **6–21**. [b] Determined by HPLC analysis. [c] 10 mol% catalyst. [d] Reaction carried out at −78 °C. [e] Reaction conducted in THF.

substituents, giving the corresponding functionalised esters in good yield (up to 86%) and high enantioselectivity (90–97% ee, **6–14**). Notable reactivity trends within this series indicate that anhydrides containing electron deficient β-aryl units give higher product conversion and isolated yields than their electron rich β-aryl counterparts (product **9**). β-Alkyl substituents within the anhydride are also tolerated (a significant advantage over the NHC-catalysed systems that typically exhibit low enantioselectivity in similar transformations),[20b] although low temperatures are necessary to achieve optimal enantioselectivity, resulting in only moderate reaction efficiency and reduced product yields (**15** and **16**). Variation of the diketone functionality was next investigated (Table 2, **17–21**). A range of substituted aryl and heteroaryl diketones participate in this reaction process, giving functionalised esters **17–21** in moderate to good yield and high enantioselectivity.[28]

Further investigations probed the stereospecificity of this asymmetric annulation protocol (Scheme 2). While (*E*,*E*)-cinnamic anhydride **3** gave functionalised ester (*S*)-**6** in 83% yield and 96% ee (Scheme 2A), (*Z*,*Z*)-cinnamic anhydride **22** gave (*R*)-**6** in reduced 41% yield and only 30% ee (Scheme 2B),[29] indicating the necessity of the (*E*)-configuration for maximum enantiocontrol.

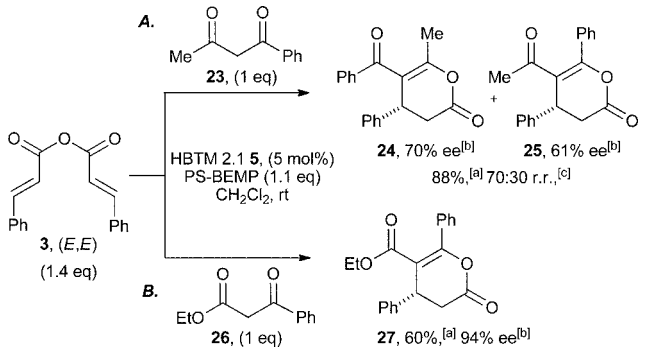


Scheme 2 Stereospecificity of asymmetric annulation process. [a]Isolated yield of **6**; [b]determined by HPLC analysis.

Subsequent studies probed the ability of non-symmetric dicarbonyls to participate in this protocol. Using cinnamic anhydride **3**, 1-phenyl-1,3-dibutanone **23** generated a 70 : 30 mixture of regioisomeric dihydropyranones **24** and **25** in 88% overall yield and 70% and 61% ee, respectively (Scheme 3A),[30] while ethyl benzoylacetate **26** gave dihydropyranone **27** in 60% isolated yield as a single regioisomer and in 94% ee (Scheme 3B).

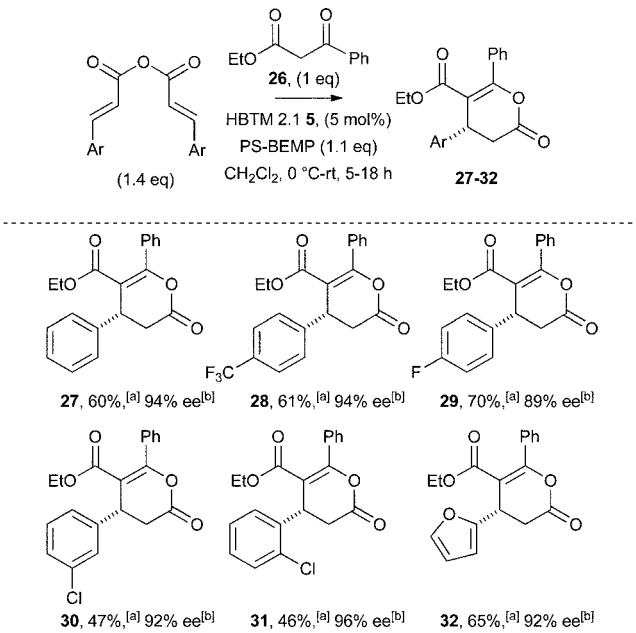
The generality of this process was next examined (Table 3), with β-aryl and β-heteroaryl substituents within the anhydride tolerated, in all cases giving the corresponding dihydropyranones **27–32** in acceptable yield (46–70%) and high ee (89–96%).[31]

Having probed the viability of this process, our attention turned to 1,3-dicarbonyl systems that are not tolerated in related NHC-catalysed processes. For example, aliphatic cyclic Michael donors such as 1,3-cyclohexanedione **33** have been reported by



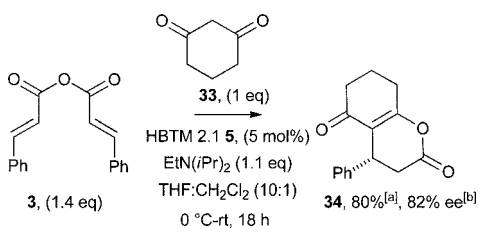
Scheme 3 Regioselectivity of annulation using unsymmetrical nucleophiles. [a]Isolated yield; [b]determined by HPLC analysis.

Table 3 Use of ethyl benzoylacetate as nucleophile

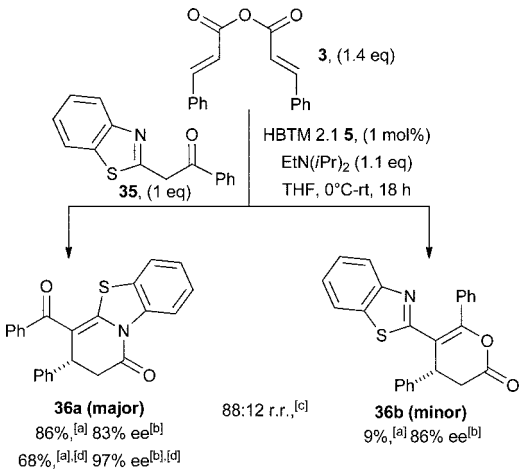


[a] Isolated yield. [b] Determined by HPLC analysis.

Bode to be ineffective in NHC-catalysis using α,β-unsaturated acyl azoliums.[21] However, in this organocatalysed process, diketone **33** demonstrated favourable reactivity and provided **34** in high yield and good enantioselectivity (Scheme 4).

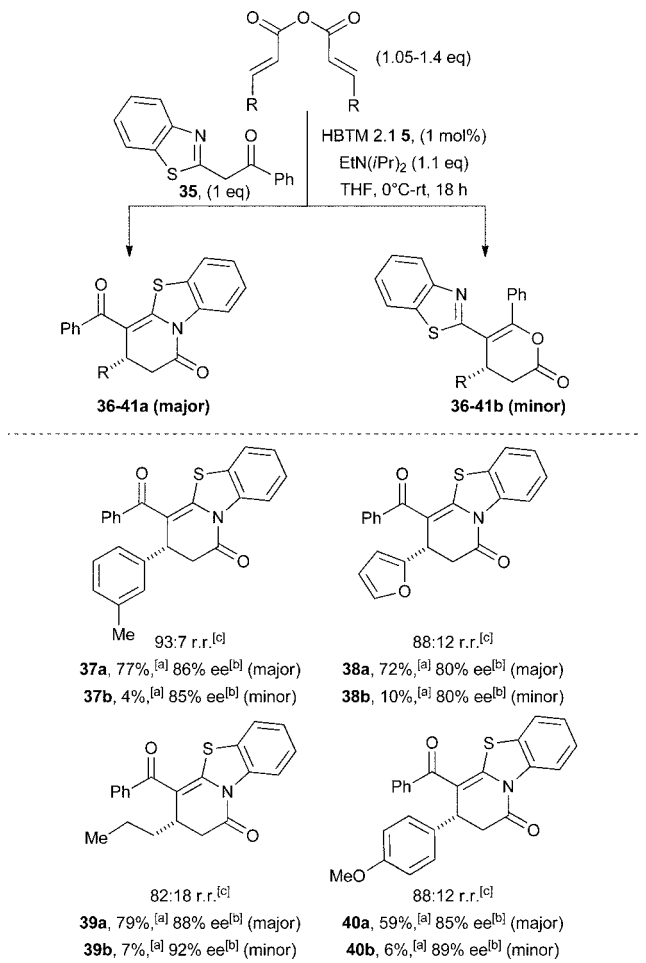


Scheme 4 1,3-Cyclohexanedione as a Michael donor. [a]Isolated yield; [b]determined by HPLC analysis.



Scheme 5 Asymmetric addition of azaaryl ketone **35**. [a]Isolated yield; [b]determined by HPLC analysis; [c]determined from ^{1}H NMR of unpurified reaction mixture; [d]following a single recrystallisation.

Table 4 Anhydride scope with azaaryl ketone **35** as a nucleophile in asymmetric annulation



[a] Isolated yield. [b] Determined by HPLC analysis. [c] Determined from ^{1}H NMR of unpurified reaction mixture.

Beyond 1,3-dicarbonyls: azaaryl ketones as nucleophiles

Encouraged by the novel and complementary reactivity of the isothiourea catalysis, the scope of this asymmetric annulation was extended beyond the use of 1,3-dicarbonyl nucleophiles. Gratifyingly, azaaryl ketone **35** proved a competent nucleophile and displayed improved reactivity compared with simple 1,3-dicarbonyls. This increased reactivity allows bench grade solvents in an open flask atmosphere to be employed, PS-BEMP can be replaced with more cost efficient EtN(*i*Pr)$_2$ and a lower catalyst loading of 1 mol% could be routinely employed. The use of this nucleophile led to intriguing regioselectivity. Cyclisation occurs preferentially through the benzothiazole nitrogen, generating dihydropyridone **36a** as the major product, in addition to dihydropyranone **36b** as the minor product (88 : 12 regioisomeric ratio). These heterocycles were readily separable by chromatography, with the major product **36a** obtained in excellent yield and high enantioselectivity (97% ee after a single recrystallisation, Scheme 5).

Next, the substrate scope with this nucleophile was examined with respect to the anhydride component (Table 4). The increased reactivity of the azaaryl ketone **35** provided a wide range of enantioenriched heterocycles in excellent yields and enantioselectivities. For example, while anhydrides bearing electron-rich and aliphatic substituents were modestly tolerated using diketone **4** (Table 2) in terms of both reactivity and enantioselectivity, the use of azaaryl ketone **35** with the same anhydrides leads to enantioenriched products in high yields under our reaction conditions (Table 4).

Mechanistic investigations

In related NHC-catalysed processes involving α,β-unsaturated acyl azolium intermediates two potential mechanistic pathways have been proposed; a Michael addition–lactonisation process with dicarbonyls, ketene acetals and enamines (favoured by Studer and Mayr)[32] or alternatively an initial 1,2-addition followed by a [3,3]-Claisen rearrangement with Kojic acid and enamine derivatives (favoured by Bode)[21] to facilitate the formation of enantioenriched products. Similarly, in our isothiourea-promoted annulation, related catalytic cycles depicted in Fig. 2(a) and (b), could potentially be responsible for the generation of the annulation products with high enantiocontrol. Both cycles involve an initial *N*-acylation of HBTM 2.1 **5** with an anhydride to generate the corresponding α,β-unsaturated acyl ammonium **41**. The *s-cis* conformation of ammonium **41** is presumably favoured, with the carbonyl oxygen hypothesised to adopt a *syn*-conformation with respect to the isothiourea S atom due to a stabilising non-bonding O–S interaction (n_o to σ^*_{C-S}).[33] In pathway (a), Michael addition[31] of diketone enolate **42** to the *Re* face of the α,β-unsaturated acyl ammonium **41** gives intermediate **43**,[34] subsequent proton transfer followed by lactonisation generates the desired dihydropyranone **44**, which can be either isolated or subsequently ring opened with MeOH to generate the ester products **45** in high ee. Alternatively, pathway (b) demonstrates that

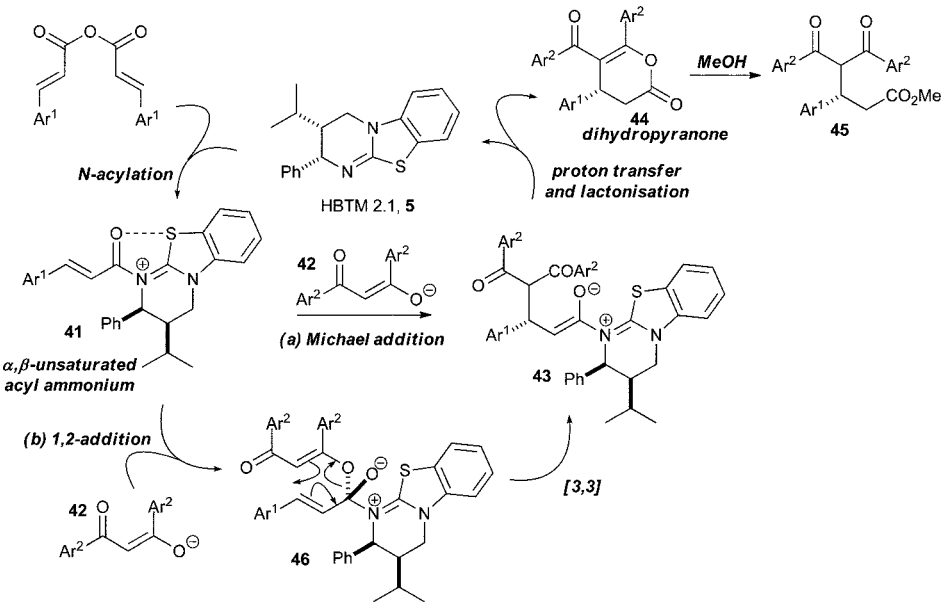
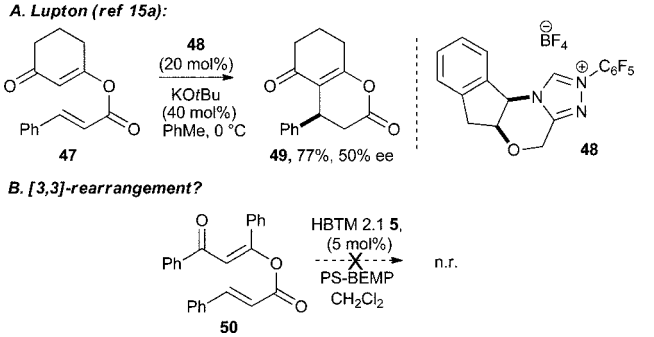


Fig. 2 Proposed mechanisms of asymmetric dihydropyranone formation *via* (a) Michael addition–lactonisation or (b) 1,2-addition, [3,3]-rearrangement.

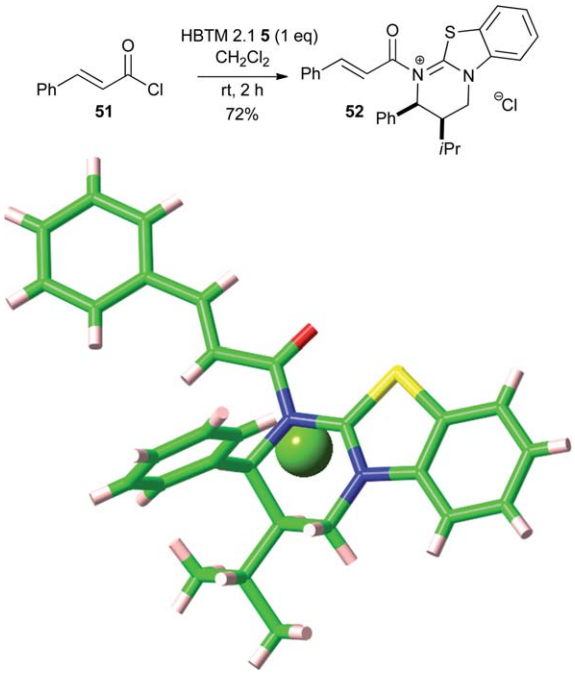
1,2-addition to the α,β-unsaturated acyl ammonium **42** to generate intermediate **46** followed by a [3,3]-rearrangement and subsequent proton transfer/lactonisation process would lead to the same enantioenriched products.

To gain insight into the favoured mechanistic pathway, potential intermediates were synthesised and subjected to the reaction conditions. Interestingly, Lupton has previously shown that 1,2-addition of NHCs to enol esters such as **47** facilitates formation of dihydropyranone **49** in the presence of NHC catalyst **48**, albeit with moderate enantioselectivity (Scheme 6A). In this regard, **50** was prepared from cinnamoyl chloride and dicarbonyl **4**. This potential [3,3]-rearrangement precursor was examined under the reaction conditions, resulting in no conversion into dihydropyranone **2** (Scheme 6B)[15a–c] after 24 h at room temperature. While this result does not rule out either mechanistic pathway, it indicates that **50** is not a likely intermediate in this process. Additionally the absence of any 1,2-addition products such as **50** in the ^{1}H NMR of all unpurified reaction mixtures provides further evidence to support this view.

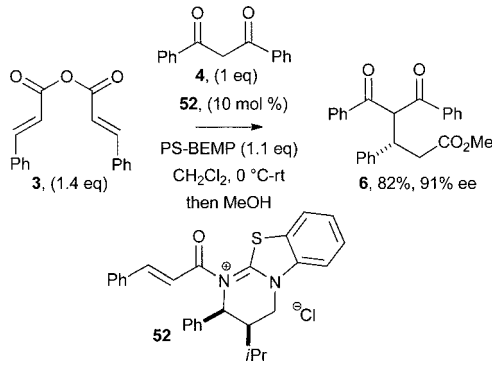


Scheme 6 Probing the mechanism.

Evidence supporting the intermediacy of an acyl ammonium species was next obtained. Treatment of *trans*-cinnamoyl chloride **51** with HBTM 2.1 **5** in CH_2Cl_2 gave the α,β-unsaturated acyl ammonium salt **52** that was isolated in high yield (Scheme 7).[35] X-ray crystallography confirmed the structure of **52** and provided further support for the *syn* geometry of the carbonyl oxygen and the isothiourea S atom, presumably due to the previously hypothesised stabilising non-bonding O–S interaction (n_o to σ^*_{C-S}).[33]



Scheme 7 Isolation and representation of the X-ray crystal structure of α,β-unsaturated acyl ammonium salt **52**.



Scheme 8 α,β-Unsaturated acyl ammonium salt **52** as organocatalyst.

The isolated acyl ammonium salt **52** was next examined as a precatalyst, employing cinammic anhydride **3** and diketone **4** under our optimised reaction conditions (Scheme 8). The functionalised ester **6** was isolated in similar yield and enantioselectivity (82% yield, 91% ee) compared with the use of organocatalyst HBTM 2.1 **5** (83% yield, 95% ee) in this process, consistent with acyl ammonium salt **52** being an intermediate in this asymmetric annulation.

At this juncture we cannot rule out any plausible mechanistic pathway that involves an α,β-unsaturated acyl ammonium ion, although we currently favour a catalytic cycle involving a Michael addition–lactonisation sequence, described in Fig. 2(a). Further mechanistic investigations and DFT calculations to provide insight into the pathway in operation are underway and will be reported in due course.

Conclusions

To conclude, HBTM 2.1 **5** promotes the asymmetric annulation of a range of nucleophiles including 1,3-diketones, β-ketoesters and azaaryl ketones to (*E*,*E*)-α,β-unsaturated anhydrides, giving either functionalised esters (upon ring opening), dihydropyranones, or dihydropyridones in good yields (up to 86%) and high enantioselectivity (up to 97% ee) *via* a postulated α,β-unsaturated acyl ammonium intermediate. Current research from this laboratory is directed toward developing alternative uses of isothioureas and other Lewis bases in asymmetric catalysis, and exploiting α,β-unsaturated acyl ammonium intermediates for a range of synthetic procedures.

Acknowledgements

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29 (*Z*,*Z*)-Cinnamic anhydride **22** was prepared by Lindlar reduction of ethyl 3-phenylpropiolate, ester hydrolysis to give (*Z*)-cinnamic acid and subsequent anhydride formation. For full experimental procedures see ESI.†

30 *In situ* ring opening by addition of methanol to dihydropyranones derived from unsymmetrical Michael donors led to a statistical mixture of diastereoisomers and so this strategy was not pursued further.

31 Addition of ethyl acetoacetate to cinnamic anhydride **3** afforded the corresponding dihydropyranone in 72% yield, 70% ee; addition of ethyl benzoylacetate to crotonic anhydride afforded the corresponding hydropyranone in 45% yield, 65% ee. See ESI† for further information.

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