Introduction

Domino reaction processes are one of the most useful strategies for the rapid generation of molecular complexity in organic synthesis.\[1\] Enantioselective organocatalysis is particularly suited to the development of complex tandem or domino processes due to the wide range of distinct activation modes accessible, the ease with which these can be combined, and the high levels of chemo- and stereoselectivity often obtained.\[2\]

Tertiary amine Lewis base-catalysed functionalisation of substrates at the carboxylic acid oxidation level can provide direct access to different catalytic intermediates that have a wide range of applications (Figure 1). To this end, enantiomerically pure catalysts based upon either the DMAP or PPY scaffolds,\[3\] cinchona alkaloids,\[4\] or isothioureas\[5\] are the most widely used. Of the intermediates directly accessible at the carboxylic acid oxidation level using these catalysts, acyl ammonium and ammonium enolates have been the most extensively studied to date and can be utilised in a number of stereoselective processes.\[6\] However, the use of α,β-unsaturated acyl ammonium intermediates generated from stable α,β-unsaturated carboxylic acid derivatives has received comparatively little attention. Seminal work in this area from Fu and co-workers used α,β-unsaturated acyl ammonium intermediates generated from a planar-chiral DMAP catalyst and α,β-unsaturated acyl fluoro-rides in [3+2] annulations with silylated indenes to form highly substituted diquinanes with good stereoselectivity (up to 92:8 d.r. and 89:11 e.r.).\[7\]

Building on this work, we reported the use of an isothiourea catalyst and homoanhydrides as α,β-unsaturated acyl ammonium precursors in Michael addition-lactonization reactions with a range of 1,3-dicarbonyls to form functionalised dihydropyridones, or esters (upon ring-opening) with high enantioselectivity (Scheme 1a).\[8\] Recent experimental and computational analysis has revealed the importance of non-bonding 1,5-S···O interactions in governing the chemo- and enantioselectivity of annulations of benzothiazoles.\[9\] Romo and co-workers subsequently used acid chlorides as α,β-unsaturated acyl ammonium precursors in enantioselective isothiourea-catalysed domino Michael addition-aldol-lactonization reactions using malonate derivatives as nucleophiles to form functionalised cyclopentanes 4 with high stereoselectivity (Scheme 1b).\[10\] Romo has also used α- and β-aminomalonates as di-nucleophiles in Michael addition-lactamization processes with α,β-unsaturated acyl ammoniums to form substituted γ-lactams and piperidones.\[10\] The α,β-unsaturated acyl ammonium intermediate can also serve as an activated dienophile in highly enantioselective organocatalytic Diels–Alder reactions to form fused γ- and δ-lactones.\[10\] Matsubara and co-workers have recently prepared enantiomerically enriched 1,5-beno-
thiazepines through reaction of 2-aminothiophenols with \( \alpha,\beta \)-unsaturated acyl ammoniums generated from mixed anhydrides and an isothiourea organocatalyst.\(^{[19]}\)

To date, these are the only reported examples investigating the use of \( \alpha,\beta \)-unsaturated acyl ammonium intermediates.\(^{[16]}\) Further studies into the reactivity and synthetic applicability of these species using readily available tertiary amine based catalysts are required to determine their versatility. To demonstrate the potential of these intermediates, in this manuscript we envisioned that introducing a second Michael acceptor into an \( \alpha,\beta \)-unsaturated acyl ammonium precursor would allow for the development of more complex domino reaction processes (Scheme 1c). Addition of suitable nucleophiles into such an \( \alpha,\beta \)-unsaturated acyl ammonium would initiate a domino process that can utilize the latent ammonium enolate and acyl ammonium reactivity present within the system. Moreover, using pro-nucleophiles that contain multiple potential sites of reactivity may further increase the molecular complexity accessible in these processes. In this case, the challenge is to generate highly chemo-, regio- and stereoselective processes that favour one specific domino reaction pathway over all others. This is particularly difficult given the multiple electrophilic and nucleophilic sites within the reactants, and such domino processes have not been previously investigated using tertiary amine based catalysis.

Herein the successful realisation of these ideas is reported using an isothiourea-derived \( \alpha,\beta \)-unsaturated acyl ammonium generated from bench-stable activated ester precursors. To the best of our knowledge, these processes are also the first demonstration of using an activated ester as an \( \alpha,\beta \)-unsaturated acyl ammonium precursor. The exact domino reaction pathway followed is dependent on the intrinsic reactivity within each class of pro-nucleophile used, which has allowed three distinct and stereodivergent processes to be developed. The fused polycyclic products obtained contain multiple contiguous stereocentres and have complex molecular topologies. Importantly, in each case the products are formed with high specificity and stereoselectivity.

### Results and Discussion

**Reactions using 1,3-dicarbonyls as nucleophiles**

Investigations into the isothiourea-catalysed domino process began with the treatment of 1,3-diphenylpropane-1,3-dione 6 with a cinnamonic acid derivative bearing an ortho-\( \alpha,\beta \)-unsaturated ketone substituent. However, no cyclisation products were observed under a range of conditions including the use of various carboxylic acid “activating” agents (such as pivaloyl chloride), isothiourea catalysts and bases.\(^{[12]}\) As in situ formation of a reactive mixed anhydride from the carboxylic acid was unsuccessful, attention turned to the use of activated esters as \( \alpha,\beta \)-unsaturated acyl ammonium precursors. While the use of a 4-nitrophenol (PNP) ester gave only traces (< 5%) of the expected cyclisation product,\(^{[13]}\) treating bench-stable 2,4,6-trichlorophenol (TCP) ester 5 with diketone 6 in the presence of the isothiourea HyperBTM 1 (20 mol%) resulted in high enantioselectivity (> 99:1 e.r.).\(^{[18]}\) Control experiments on isolated samples of each isomer showed that the products do not interconvert under the reaction conditions. Further optimisation of this domino process showed that isothioureas such as tetramisole hydrochloride (TM-HCl) 8 and benzotetramisole (BTM) 9 were not competent catalysts, returning only starting materials (Table 1, entries 2 and 3). Changing the solvent and reaction stoichiometry had an impact on both yield and selectivity (Table 1, entries 4–6), with the optimal conditions using two equivalents of both diketone 6 and PS-BEMP in THF at room temperature giving fused 1,2,3-substituted indane 7a as a single diastereoisomer in 60% yield and > 99:1 e.r. (Table 1, entry 6). Under these conditions, no base-promoted background reaction was observed in the presence of the catalyst (Table 1, entry 7). Reducing the catalyst loading (5 or 10 mol%) still gave 7a with excellent selectivity, but led to a reduction in isolated yield (48 and 53%, respectively).

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**Scheme 1.** \( \alpha,\beta \)-Unsaturated acyl ammoniums in domino organocatalytic processes.

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practicality of the process was demonstrated by performing the reaction on a 5 mmol scale, providing 1.2 g of indane 7a as a single stereoisomer (Table 1, entry 8).

The scope and limitations of the domino process was first explored through variation of the nucleophile (Table 2). Symmetrical aryl substituted diketones bearing electron-rich, halogen and heterocyclic substituents worked well under the previously optimised conditions, giving fused indanes 10a–12a in good yields and excellent diastereo- and enantioselectivity.

The absolute and relative configuration of 12a was confirmed by X-ray crystallographic analysis, with all other products in this series assigned by analogy.29 The use of non-aryl substituted diketones such as acetylacetone led to a slight drop in product selectivity and a significant reduction in enantioselectivity for 13a (62.5:37.5 e.r.), although the diastereoselectivity remained high. A control experiment in the absence of HyperBTM 1 did not lead to product formation, demonstrating that a racemic base-promoted background reaction is not responsible for the observed drop in enantioselectivity. Malonates are also competent nucleophiles in this process, selectively forming fused products 14a and 15a with high diastereoselectivity, but with slightly reduced enantioselectivity. The treatment of 5 with non-symmetrical ethyl benzoylacetate gave indane 16 in 74% yield, although the additional sterogenic centre was only modestly controlled leading to a 75:25 mixture of diastereoisomers.

Next, a wide range of substituted $\alpha$$\beta$-unsaturated TCP esters was subjected to the previously optimised reaction conditions using aryl 1,3-diketones as nucleophiles (Table 3). The various TCP esters were readily synthesised in four high-yield.

| Entry | Cat. | Solvent | Yield [%] | 7a/7b | e.r. | 7a/7b | e.r. |
|-------|------|---------|----------|-------|------|-------|------|
| 1     | 1:1:1| CH$_2$Cl$_2$| 46       | 75:25 | 97.5:2.5 |
| 2     | 1:1:1| CH$_2$Cl$_2$| trace    | –     | –     | 99:1  |
| 3     | 1:1:1| CH$_2$Cl$_2$| trace    | –     | –     | 95:5:4.5 |
| 4     | 1:1:1| MeCN     | 62       | 86:14 | 96.5:2.5 |
| 5     | 1:2:2| MeCN     | 70       | 91:9  | 95:5:4.5 |
| 6     | 1:2:2| THF      | 60       | >95:5 | >99:1 |
| 7     | 1:2:2| THF      | –        | –     | –     | –     |
| 8     | 1:2:2| THF      | 57       | >95:5 | >99:1 |

[a] Reactions performed on 0.1 mmol scale. [b] Combined yield. [c] The a/b ratio was determined by $^1$H NMR spectroscopic analysis of the crude reaction product. [d] Determined by HPLC analysis. [e] Reaction performed on a 5 mmol scale.

The reaction mechanism using 1,3-dicarbonyls as nucleophiles is proposed to proceed through a domino Michael-Michael-lactonization process (Scheme 2a). Nucleophilic addition of HyperBTM 1 into TCP ester 5 generates an $\alpha$$\beta$-unsaturated acyl ammonium intermediate 29. Michael addition of the enolate of 1,3-dicarbonyl 6 onto 29 generates ammonium enolate 30, which undergoes intramolecular Michael addition onto the pendent enone. Lactonization of the resulting enolate onto
the acyl ammonium releases polycyclic product 7a and regenerates the catalyst. The observed stereochemical outcome is proposed to arise from an initial Michael addition onto the Re-face of α,β-unsaturated acyl ammonium 29, which is conformationally locked due to a stabilising non-bonding O–S interaction (νO to α∗C–S), with the Si-face effectively blocked by the stereodirecting groups on the catalyst.\[20\] Evidence for such an O–S interaction has previously been obtained both in the solid-state, through X-ray analysis of an α,β-unsaturated acyl isothiourea salt,\[8\] and computationally through DFT calculations of possible transition states for a Diels–Alder reaction using an α,β-unsaturated acyl ammonium.\[9c\] Subsequent intramolecular Michael addition of ammonium enolate 30 proceeds under substrate control, with the 1,3-dicarbonyl, ammonium enolate and enone all adopting pseudo-equatorial positions in the five-membered pre-transition state assembly 32 (Scheme 2b). Cyclisation under catalyst control is presumably disfavoured due to the presence of A13 strain between the 1,3-dicarbonyl substituent and the ammonium enolate.\[21\]

Reactions using acyl benzothiazoles as nucleophiles

Having explored the use of various 1,3-dicarbonyls, the use of acyl benzothiazoles as an alternative pro-nucleophile class in the domino process was investigated. Reacting α,β-unsaturated TCP ester 5 with 2-phenacyl benzothiazole 34 under the previously optimised conditions using HyperBTM 1 (20 mol%) as the catalyst gave a separable 89:11 mixture of functionalised polycyclic products 35a and 35b in 53% yield (Scheme 3).

Table 3. Variation of the Michael acceptor with 1,3-diketones.[a–e]

| Entry | Michael Acceptor | a/b Ratio | d.r. | e.r. |
|-------|-----------------|----------|------|------|
| 17    | Ph            | 67%      | >95.5 d.r. | 99:1 e.r. |
| 18    | Ph            | 55%      | >95.5 d.r. | 99:1 e.r. |
| 19    | Ph            | 46%      | >95.5 d.r. | 99:1 e.r. |
| 20    | Ph            | 74%      | >95.5 d.r. | 99:1 e.r. |
| 21    | Ph            | 71%      | >95.5 d.r. | 99:1 e.r. |
| 22    | Ph            | 69%      | >95.5 d.r. | 99:1 e.r. |
| 23    | Ph            | 67%      | >95.5 d.r. | 97:3 e.r. |
| 24    | Ph            | 65%      | >95.5 d.r. | 97:3 e.r. |
| 25    | Ph            | 67%      | >95.5 d.r. | 96:4 e.r. |
| 26    | Ph            | 65%      | >95.5 d.r. | 96:3:5 e.r. |
| 27    | Ph            | 79%      | >95:5 d.r. | 99:1 e.r. |
| 28    | Ph            | 62%      | >95:5 d.r. | 97:5:2.5 e.r. |

(a) Reactions performed on 0.1 mmol scale. (b) Combined yield. (c) The a/b ratio was determined by 1H NMR spectroscopic analysis of the crude reaction product. (d) The d.r. was determined by 1H NMR spectroscopic analysis. (e) The e.r. was determined by HPLC analysis.
In this case, major product 35a results from preferential cyclisation through the benzothiazole nitrogen, which is consistent with previous observations using this class of nucleophile. Interestingly, while the diastere- and enantiomeric selectivity of this process remain high (>95:5 d.r., 94:6 e.r.), the relative configuration around the fused indane 35a is different to that observed within the major product from the reaction using 1,3-dicarbonyls. The relative configuration of minor product 35b could not be determined, although it is formed as a racemate suggesting that it may arise from a base-mediated background process. A control experiment in the absence of HyperBTM 1 confirmed the presence of a base-promoted reaction in this case.

Intrigued by the change in constitution and configuration within the major product, the scope of the domino process using various acyl benzothiazoles as nucleophiles was explored (Table 4). Substitution within the benzenoid ring of the α,β-unsaturated ester was possible, although the presence of a methyl substituent led to lower enantioselectivity (82:18 e.r. for 36a). The presence of an aryl enone substituent worked particularly well, forming indane 38a in 83% yield with high selectivity (93:7 a/b) and excellent stereoselectivity (>95:5 d.r., 97:3 e.r.). Within the acyl benzothiazole, halogen substitution around the benzenoid ring gave products 39a and 40a in good yields and high stereoselectivity. A lower yield was obtained for 41a bearing an electron-donating methoxy substituent (20%), although the stereocontrol remained high. The relative and absolute configuration of 41a was confirmed by X-ray crystallographic analysis with all other products assigned by analogy. Various 2-arylacyl benzothiazole substituents were also tolerated, forming polycyclic products 42a–44a with high product selectivity and with good diastereo- and enantiocontrol.

The stereodivergence observed in the major products obtained from the reactions using 2-acyl benzothiazoles compared with 1,3-dicarbonyls can be rationalised through the operation of an alternative domino Michael-lactamisation-Michael pathway (Scheme 4a). After initial Michael addition onto α,β-unsaturated acyl ammonium 29 the resulting ammonium enolate 45 undergoes preferential proton transfer to give acyl ammonium 46. Lactamisation of the benzothiazole nitrogen onto the acyl ammonium generates dihydropyridone 47 and releas-
es the catalyst. Subsequent base-mediated cyclisation of 47 generates the observed polycyclic indane 35a. In this case, the intramolecular Michael addition occurs through the conformationally restricted enolate of dihydropyridone 47, with the enone adopting a pseudo-equatorial position in the forming indane ring (Scheme 4b).

Reactions using acyl benzimidazoles as nucleophiles

As acyl benzothiazoles had given a distinct domino reaction pathway, the use of alternative acyl benzazoles was investigated. While treatment of 2-phenacyl benzoxazole with α,β-unsaturated TCP ester 5 under the previously optimised conditions led to a complex isomeric mixture, reaction with 2-phenacyl benzimidazole 53 gave a single major product isolated in 83% yield (Scheme 6). Further characterisation revealed its structure to be fused polycycle 54 containing three contiguous stereocentres, including one quaternary stereocentre. Although 54 was formed as a single diastereoisomer, the enantioselectivity was low (62:38 e.r.).

Intrigued by this observation and the possibility of accessing another distinct domino pathway, the reaction with 2-phenacyl benzimidazole 53 was optimised (Table 5). A control experiment in the absence of catalyst also led to product 54 in 79% yield and >95:5 d.r. (Table 5, entry 1), with X-ray crystallographic analysis confirming the structural assignment and relative configuration. The presence of a significant racemic base-promoted background reaction accounts for the low enantioselectivity observed in the presence of HyperBTM 1. Consequently, the racemic base-promoted domino reaction of 5 with 53 was first studied. Weaker organic bases such as Pr₂NEt led to no product formation, but addition of DMAP (20 mol%) gave 31% of 54 (Table 5, entries 2 and 3). The use of the amidine base DBU led to a complex mixture (Table 5, entry 4), therefore PS-BEMP was chosen for further study. The domino process was more efficient in CH₂Cl₂ compared with either THF or MeCN and the reaction stoichiometry could be reduced to 1.5 equivalents of both 53 and PS-BEMP, giving 54 in 90% yield as a single diastereoisomer (Table 5, entries 5–7). The reaction could be performed on a 3.5 mmol scale, leading to the isolation of 1.3 g of used polycycle 54 in 84% yield (Table 5, entry 8).

The scope and limitations of this process were explored through variation of both the acyl benzimidazole and the α,β-unsaturated TCP ester (Table 6). Various 2-arylacyl benzimidazoles containing either electron-donating, electron-withdrawing or halogen substituents were tolerated, forming fused indanes 55–60 in generally good yield and excellent diastereoselectivity. Introduction of a 2-furfyl substituent gave product 61 in 68% yield, although the diastereoselectivity was reduced...
Substitution around the benzimidazole ring was also well tolerated, giving selective access to polycycles.

The introduction of substituents within the benzenoid ring of the αβ-unsaturated TCP ester gave the corresponding products 65 and 66 in excellent yield as single diastereoisomers. In contrast with the reactions using acyl benzothiazoles, only an electron-rich aryl enone substituent could be incorporated, forming product 68 in 80% yield. The presence of either electron-withdrawing or halogen substituted aromatic rings on the enone led to mixtures of products and low yields. Notably, the pendent enone could be replaced with an αβ-unsaturated methyl ester, giving the corresponding indane 69 in 79% yield with excellent selectivity.

Having demonstrated a wide scope for the diastereoselective domino process using benzimidazoles as nucleophiles, the possibility of an isothioura-catalysed enantioselective variant was revisited. The reaction of TCP ester 5 and benzimidazole 53 under the previously optimised conditions with the addition of HyperBTM 1 (20 mol %) gave product 54 as a single diastereoisomer, but with low enantioselectivity (Table 7, entry 1). Lowering the temperature to 0 °C led to an improvement, with 54 formed in 70.5:29.5 e.r. (Table 7, entry 2). Changing the base used also had an impact on enantioselectivity. While DBU gave a complex mixture, the use of 2,6-lutidine gave product 54 in an enhanced 83:17 e.r. (Table 7, entries 3 and 4). Finally, using iPr₂NEt allowed 54 to be isolated in 60% yield as a single diastereoisomer in 88:12 e.r. (Table 7, entry 5).

**Table 5. Reaction optimisation.**

| Entry | Base Solvent | 5/53/base | t [h] | Yield [%] | d.r. [a] |
|-------|--------------|-----------|-------|-----------|---------|
| 1     | PS-BEMP THF  | 1:2:2     | 16    | 79        | >95:5   |
| 2     | iPr₂NEt THF  | 1:2:2     | 16    | trace     | –       |
| 3     | iPr₂NEt THF  | 1:2:2     | 16    | 31        | >95:5   |
| 4     | DBU THF      | 1:2:2     | 16    | –         | –       |
| 5     | PS-BEMP MeCN | 1:2:2     | 16    | 56        | >95:5   |
| 6     | PS-BEMP CH₂Cl₂ | 1:2:2     | 24    | 90        | >95:5   |
| 7     | PS-BEMP CH₂Cl₂ | 1:1:2:1:2 | 40    | 97 (90)   | >95:5   |
| 8     | PS-BEMP CH₂Cl₂ | 1:1:2:1:2 | 40    | (84)      | >95:5   |

[a] Reactions performed on 0.1 mmol scale. [b] NMR yield using 1,4-dinitrobenzene as an internal standard. [c] Determined by 1H NMR spectroscopic analysis. [d] Reaction using 20 mol % DMAP. [e] Isolated yield in parentheses. [f] Reaction performed on a 3.5 mmol scale.

**Table 6. Substrate scope using acyl benzimidazoles as nucleophiles.**

| R¹ | R² | TCP | PS-BEMP (1.5 equiv) CH₂Cl₂, RT, 40 h | R³ |
|----|----|-----|------------------------------------|----|
| (±)-55 | OMe | 2,4,6-Cl₃C₆H₃ | + | (±)-54 |
| (±)-56 | NO₂ | | | (±)-57 |
| (±)-57 | CF₃ | | | (±)-58 |
| (±)-58 | Cl | | | (±)-59 |
| (±)-59 | Br | | | (±)-60 |
| (±)-60 | Ph | | | (±)-61 |
| (±)-61 | Ph | | | (±)-62 |
| (±)-62 | Ph | | | (±)-63 |
| (±)-63 | Ph | | | (±)-64 |
| (±)-64 | Ph | | | (±)-65 |
| (±)-65 | Ph | | | (±)-66 |
| (±)-66 | Ph | | | (±)-67 |
| (±)-67 | Ph | | | (±)-68 |
| (±)-68 | Ph | | | (±)-69 |

[a] Reactions performed on 0.1 mmol scale. [b] The d.r. was determined by 1H NMR spectroscopic analysis.
The newly optimised conditions for the HyperBTM 1-catalysed reaction using benzimidazoles were applied to the enantioselective synthesis of a subset of the fused polycycles made previously (Table 8). Structural variation within both the benzimidazole and α,β-unsaturated TCP ester was tolerated, forming the products in generally good yields with excellent diastereoselectivity and comparable levels of enantioselectivity in each case. The absolute and relative configuration of fused indane 55 was confirmed through X-ray crystallographic analysis of a recrystallised sample (98.5:1.5 e.r.)[26] with all other products assigned by analogy.

Mechanistically, the reactivity and stereoselectivity observed for the reactions using benzimidazoles can be rationalised by the Michael-lactamization-Michael domino pathway depicted in Scheme 7a. Michael addition occurs on the Re-face of α,β-unsaturated acyl ammonium 29, with subsequent proton transfer and lactamization of the resulting acyl ammonium 71 generating fused dihydropyridone 72 and releasing the catalyst.

Table 7. Optimisation of enantioselective reaction.[a–c]

| Entry | Base | T [°C] | Yield [%][b] | d.r.[c] | e.r.[c] |
|-------|------|--------|-------------|--------|--------|
| 1     | PS-BEMP | RT | 97          | >95:5   | 57:43  |
| 2     | PS-BEMP | 0   | 65          | >95:5   | 70:5:29.5 |
| 3     | DBU   | 0–10 | –          | –      | –      |
| 4     | 2,6-lutidine | 0–10 | 70          | >95:5   | 83:17  |
| 5     | iPr₂NEt | 0–10 | 68 (60)[d]  | >95:5   | 88:12  |

[a] Reactions performed on 0.1 mmol scale. [b] NMR yield using 1,4-dinitrobenzene as an internal standard. [c] Determined by 1H NMR spectroscopic analysis. [d] Determined by HPLC analysis. [e] Isolated yield in parentheses.

Table 8. Scope of the enantioselective process.[a–c]

| Entry | Base | R¹ | R² | T [°C] | Yield [%][b] | d.r.[c] | e.r.[c] |
|-------|------|----|----|--------|-------------|--------|--------|
| 54    | Ph   | Ph | Ph | 0–10   | 60%         | >95:5 d.r., 88:12 e.r. |
| 55    | iPr  | OMe| OMe| 0–10   | 49%         | >95:5 d.r., 85:15 e.r. |

[a] Reactions performed on 0.1 mmol scale. [b] The d.r. was determined by 1H NMR spectroscopic analysis. [c] The e.r. was determined by HPLC analysis. [d] The e.r. was obtained upon single recrystallisation.

Conclusions

α,β-unsaturated acyl ammonium intermediates generated from an isothiocure catalyst and bench-stable α,β-unsaturated TCP esters bearing pendent Michael acceptors undergo various
enantioselective nucleophile-dependent domino reactions. Three divergent processes are observed by using either 1,3-dicarbonyls, acyl benzothiazoles, or acyl benzimidazoles as pro-nucleophiles, forming a range of complex fused polycycles containing multiple contiguous stereocentres with high selectivity and stereocontrol. The different domino processes make use of multiple catalytic intermediates, including α,β-unsaturated acyl ammonium, ammonium enolate and acyl ammoniums and rely on the intrinsic differences in reactivity within each class of pro-nucleophile to form the products with high selectivity. Current work in this laboratory is aimed at further developing Lewis base-catalysed enantioselective transformations.

General procedure for the Michael-Lactonization reaction with 1,3-dicarbonyls

HyperBTM 1 (20 mol%), PS-BEMP (2 equiv), and the appropriate 1,3-dicarbonyl (2 equiv) were added to a solution of the appropriate α,β-unsaturated TCP ester in anhydrous THF (0.4 M) at room temperature. The reaction mixture was stirred for 48 h before being filtered to remove the base and concentrated in vacuo. The crude product was purified by column chromatography (petrol/EtOAc) on silica gel to give products of approximately 95% purity. Analytically pure samples could be obtained through a second chromatographic purification using CH₂Cl₂ as eluent.

General procedure for the Michael-lactamization-Michael reaction with acyl benzothiazoles

HyperBTM 1 (20 mol%), PS-BEMP (2 equiv), and the appropriate acyl benzothiazole (2 equiv) were added to a solution of the appropriate α,β-unsaturated TCP ester in anhydrous THF (0.4 M) at room temperature. The reaction mixture was stirred for 48 h before being filtered to remove the base and concentrated in vacuo. The crude product was purified by column chromatography (petrol/EtOAc) on silica gel to give products of approximately 95% purity. Analytically pure samples could be obtained through a second chromatographic purification using CH₂Cl₂ as eluent.

General procedure for the diastereoselective Michael-lactamization-Michael reaction with acyl benzimidazoles

PS-BEMP (1.5 equiv), and the appropriate acyl benzothiazole (2 equiv) were added to a solution of the appropriate α,β-unsaturated TCP ester in anhydrous CH₂Cl₂ (0.4 M) at room temperature. The reaction mixture was stirred for 40 h before being filtered to remove the base and concentrated in vacuo. The crude product was purified by column chromatography (petrol/EtOAc) on silica gel to give products of approximately 95% purity. Analytically pure samples could be obtained through a second chromatographic purification using CH₂Cl₂ as eluent.

For the synthesis of starting materials, full characterisation data, NMR spectra, and HPLC traces, see the Supporting Information.

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CCDC 1473024 (±)-54 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

For further details of the reaction optimisation, see the Supporting Information.

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