Isothiourea-Catalysed Acylative Dynamic Kinetic Resolution of Tetra-substituted Morpholinone and Benzoxazinone Lactols

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Abstract: The development of methods to allow the selective acylative dynamic kinetic resolution (DKR) of tetra-substituted lactols is a recognised synthetic challenge. In this manuscript, a highly enantioselective isothiourea-catalysed acylative DKR of tetra-substituted morpholinone and benzoxazinone-derived lactols is reported. The scope and limitations of this methodology have been developed, with high enantioselectivity and good to excellent yields (up to 89%, 99:1 er) observed across a broad range of substrate derivatives incorporating substitution at N(4) and C(2), di- and spirocyclic substitution at C(5)- and C(6)-position, as well as benzannulation (>35 examples in total). The DKR process is amenable to scale-up on a 1 g laboratory scale. The factors leading to high selectivity in this DKR process have been probed through computation, with an N-C=O•••isothiouronium interaction identified as key to producing ester products in highly enantioenriched form.

Introduction: Kinetic resolution is a widely developed process that has been extensively used for industrial and academic applications to allow the effective preparation of enantiomerically pure compounds.[1] Despite its widespread use, a recognised inherent drawback is that the theoretical maximum yield of a single product enantiomer from a racemate is 50%. This limitation can be overcome by a using a dynamic kinetic resolution (DKR) approach, that necessitates the individual enantiomers of the racemic starting material to interconvert (enantiomerization) at a timescale compatible with a subsequent enantioselective derivatization event (such as acylation).[1v] Current state-of-the art DKRs commonly use *secondary* alcohols or *tri*-substituted lactols (that contain a H-substituent at the carbinol carbon), with enantiomerization promoted through reversible dehydrogenation/hydrogenation (Fig 1A&B) or intramolecular ring closure/ring opening (Fig 1C&D). As representative examples of these approaches, Bäckvall has shown that a Ru-based catalyst can promote the enantiomerization of racemic secondary alcohols (Fig 1A) via a planar carbonyl intermediate, which is compatible with the subsequent enzymatic acylative KR.[1q, 1s, 2] Alternatively treatment of racemic tri-substituted lactol with an isothiourea catalyst and anhydride leads to ester product in high yield and enantioselectivity with enantiomerization achieved via an achiral ring-opened intermediate (Fig 1B).[3] The widely recognized remaining challenge in this area that has not been realized to date is to extend the DKR approach to tetra-substituted lactol substrates (where none of the substituents at the carbinol are H) (Fig 1C). To the best of our knowledge only a single report from Ye and co-workers utilising NHC catalysed enantioselective acylative DKR of benzosultam derived trifluoromethyl substituted hemi-aminols has been reported in this area to date.[4] Although excellent enantioselectivity was observed, this methodology was limited by the need for C(3)-perfluorinated substituents at the carbinol centre, and requires a stoichiometric oxidant (3,3′,5,5′-tetra-*tert*-butyldiphenoquinone, DQ) for reactivity (Fig 1D).

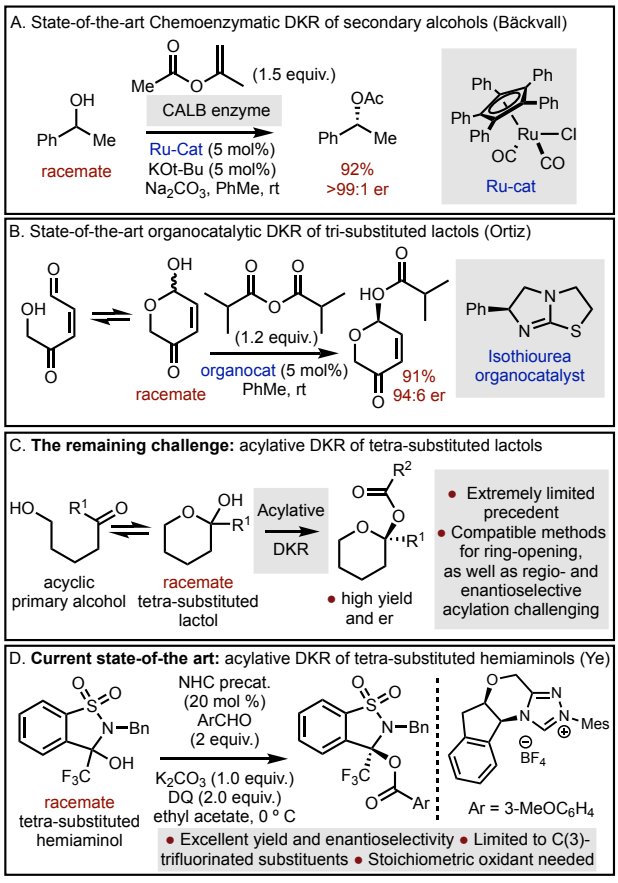


Figure 1: DKR approaches and the remaining challenge: effective DKR of tetra-substituted lactols.

Nitrogen-containing heterocycles are core features within biologically relevant pharmaceuticals,[5] agrochemicals,[6] and natural products[7] with 59% of US FDA approved small-molecule

drugs containing a nitrogen heterocycle.[5g] Within this field, the morpholine skeleton is widely considered a privileged scaffold for medicinal chemistry,[5d] and is recognised as being in the top 25 carbo- and heterocyclic ring systems that are incorporated within drug molecules.[5c, 5g, 5h] Within the morpholine family the morpholin-3-one lactol motif is a core constituent of various natural products such as Acortatarin A[8] but is also present in σ_1- and μ-opioid receptor binding molecules,[9] as well as neurokinin receptor antagonists (Fig 2A).[10] Benzannulation of morpholine leads to benzoxazine derivatives that are known to possess antimicrobial, and antibacterial activity among others.[11] They are of significant medicinal interest with derivatives displaying anti-Alzehimer and anticancer properties among others,[12] as well as being of agricultural interest.[13] Similarly, 1,4-benzoxazine derived lactols are the core heterocycle of Tonghaoxu analogues[14] and plant growth inhibitors,[15] while hydroxylated benzoxazinones such as $GHDM_2BOA$[13a, 16] are natural products found in their glycoside form.[13a, 16] As such the development of new methods for the preparation of enantioenriched morpholine and benzoxazine derivatives is of widespread interest.

In recent years the use of isothioureas as enantioselective Lewis base catalysts has been well established and applied to a range of reactions employing acyl ammonium,[17] C(1)-ammonium enolates,[18] and α,β-unsaturated acyl ammonium intermediates.[19] In previous work we have applied the isothiourea HyperBTM in the KR of both tertiary heterocyclic[20] and acyclic alcohols.[21] In the heterocyclic alcohol case the reactivity and selectivity observed in were rationalised by a combination of computation and experimental evidence, that identified the significance of a key substrate C=O•••isothiouronium interaction (alongside 1,5-O•••S and C-H•••O contacts) as being essential to achieve effective enantiodiscrimination in this KR process (Fig 2B). [20a, 22] Utilising this precedent, we considered that an effective acylative DKR of tetra-substituted morpholinones and benzoxazinones could be achieved using isothiourea catalysis. Reversible *intra*molecular ring-opening/ring closing of the heterocyclic scaffold would be used as an enantiomerization strategy,[23] combined with isothiourea-promoted enantioselective acylation (incorporating the key substrate C=O•••isothiouronium interaction for selectivity)[3, 24] to generate medicinally relevant N-heterocycles in enantiomerically pure form (Fig 2C). At the onset of these studies the key challenges to overcome for an effective solution were (i) potential competition between acylation of the primary alcohol of the ring-opened species with acylation of the sterically hindered tetra-substituted lactol; (ii) the acylation catalyst is required to discriminate between enantiomers bearing three non-hydrogen substituents at the tetra-substituted carbinol centre; (iii) enantioselective acylation needs to be coupled with efficient enantiomerization for a DKR to work effectively.[1v] In this manuscript the DKR of a range of morpholinone and benzoxazinone derived tetra-substituted lactols is developed, with the scope and limitations of this process fully explored with respect to competitive acylation of a ring-opened derivative as well as enantioselectivity. DFT computational studies highlight the importance of the adjacent carbonyl group to the carbinol stereocentre as a key enantiorecognition motif that leads to products in high er.

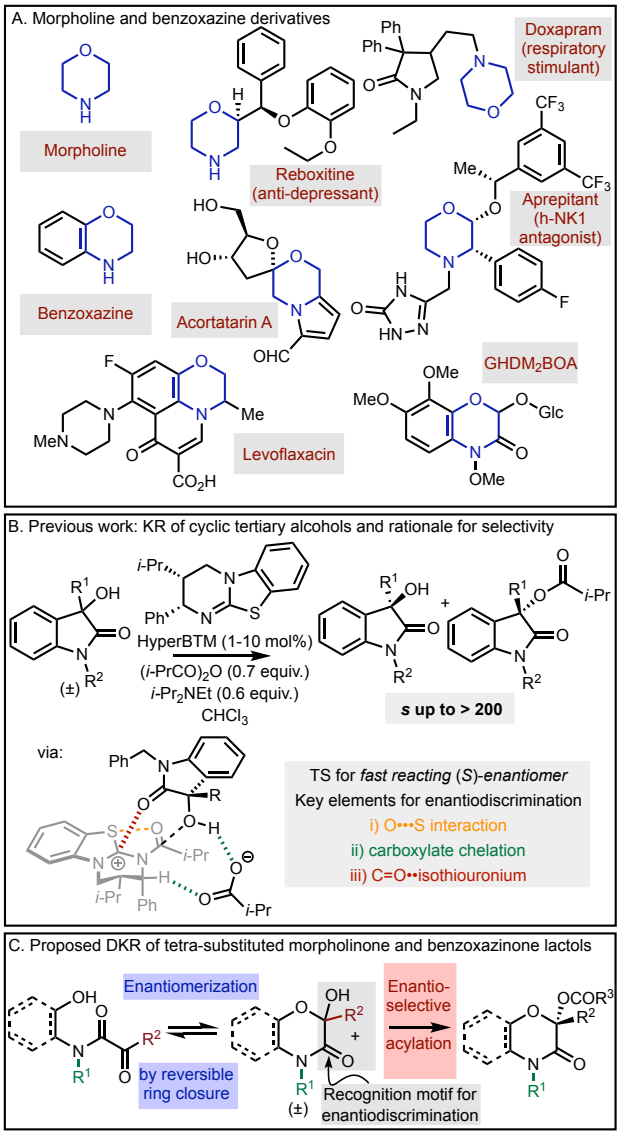


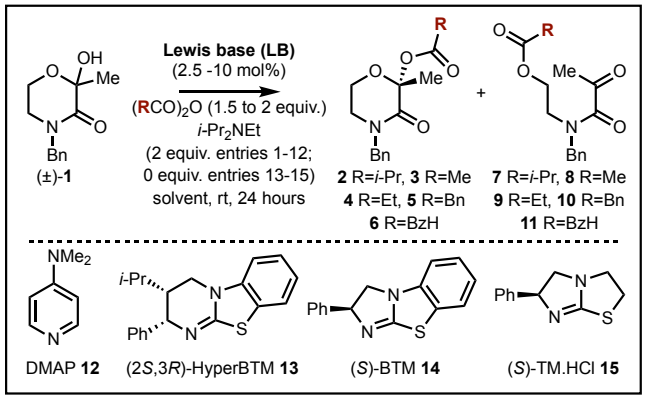
Figure 2: A: Morpholine and benzoxazine derivatives. B. Previous kinetic resolution of tertiary alcohols. C. The DKR approach in this manuscript.

Results and Discussion:

Optimisation of DKR in a model system:

To investigate the feasibility of the proposed process, the acylation of morpholinone alcohol **1** was explored as a model substrate (Table 1). Initial studies used DMAP (10 mol%) as the Lewis base, isobutyric anhydride as the acyl source and *i*-Pr_2NEt as the base in $CHCl_3$, giving a 75:25 mixture of the desired ring-closed acylated heterocycle **2** to ring-opening dicarbonyl compound **7** (entry 1). As proof-of-principle towards the proposed DKR process, treatment of **1** with the isothiourea (2*S*,3*R*)-HyperBTM **13** (10 mol%), isobutyric anhydride (2 equiv.), *i*-Pr_2NEt (2 equiv.) in $CHCl_3$ gave an improved 91:9 mixture of the desired heterocycle **2** (97:3 er) to the ring-opened product **7** (entry 2). Evaluation of the alternative isothiourea catalysts (*S*)-BTM **14** and (*S*)-tetramisole **15** gave significantly reduced conversion to acylated products, giving **2** in <15% conversion and with reduced enantioselectivity (11:89 and 9:91 respectively, entries 3 and 4). Variation of both solvent and anhydride using (2*S*,3*R*)-HyperBTM **13** showed that while high enantioselectivity for ester **2** was

generally maintained, the ratio of acylated heterocycle to ring-opened ester was significantly affected (entries 5-14). For example, THF gave the highest proportion (25%) of ring-opened product (entry 5), while toluene gave the highest proportion of the desired product (93:7 ratio), giving **2** in 80% yield and 97:3 er (entry 8). In toluene, acetic and propionic anhydride gave reasonable product enantioselectivity but a 75:25 ratio of acylated heterocycle to ring-opened ester products, while 2,2-diphenylacetic anhydride gave a 50:50 mixture of products, with **2** in reduced enantioselectivity (entry 12). Further optimization using toluene as the reaction solvent showed that decreasing the catalyst loading and anhydride stoichiometry was possible alongside further simplification of the reaction conditions through the removal of base (entries 13-15). Using 5 mol% of HyperBTM (entry 14) was considered optimal, giving **2** in 80% isolated yield and 97:3 er.



Entry	LB (mol %)	R (equiv.)	Solvent	Yield[a]	ratio[a]	er[b]
1	**12** (10)	*i*-Pr (2.0)	$CHCl_3$	97	75:25	50:50
2	**13** (10)	*i*-Pr (2.0)	$CHCl_3$	97	91:9	97:3
3	**14** (10)	*i*-Pr (2.0)	$CHCl_3$	13	90:10	11:89
4	**15** (10)	*i*-Pr (2.0)	$CHCl_3$	12	90:10	9:91
5	**13** (10)	*i*-Pr (2.0)	THF	>99	75:25	94:6
6	**13** (10)	*i*-Pr (2.0)	CH_2Cl_2	>99	87:13	94:6
7	**13** (10)	*i*-Pr (2.0)	EtOAc	>99	84:16	95:5
8	**13** (10)	*i*-Pr (2.0)	PhMe	>99	93:7	97:3
9	**13** (10)	Me (2.0)	PhMe	>99	75:25	90:10
10	**13** (10)	Et (2.0)	PhMe	>99	75:25	93:7
11	**13** (10)	Bn (2.0)	PhMe	92	75:25	91:9
12	**13** (10)	Bzh (2.0)	PhMe	>99	50:50	85:15
13	**13** (10)	*i*-Pr (1.5)	PhMe	>99	91:9	97:3
14	**13** (5)	*i*-Pr (1.5)	PhMe	96	91:9	97:3
15[c]	**13** (2.5)	*i*-Pr (1.5)	PhMe	86	91:9	97:3

Table 1: [a]. Combined product yield and product ratio (of lactol ester: acyclic ester) calculated from ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [b]. measured by HPLC analysis on a chiral stationary phase. [c]. Reaction carried out at [0.33] M concentration.

Scope and Limitations:

The scope and limitations of the developed process were subsequently investigated. Variation of the steric and electronic properties of the C(2)-substituent was predicted to challenge competition between acylation of the primary alcohol of the ring-opened species with acylation of the sterically hindered tetra-substituted lactol (Figure 3A). This optimized reaction process was amenable to scale-up, with the DKR of lactol **1** carried out on a 4.5 mmol (1 g) scale, giving **2** in 78% isolated yield and 97:3 er. With aliphatic C(2)-substituents, variation of the carbon chain from C(2)-methyl to C(2)-ethyl maintained excellent product yield and enantioselectivity (**17**, 68%, 98:2 er) with 15% of the undesired acyclic product observed. The introduction of a C(2)-allyl substituent was tolerated, giving **19** (86%, 94:6 er) with <5% of the corresponding acyclic product observed. A C(2)-benzyl substituent gave excellent product yield and enantioselectivity (85%, 99:1 er), with <5% of the corresponding di-acylated acylic product **22** observed. Variation of the benzylic aryl substituent was readily tolerated, with the corresponding 4-*t*-BuC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4 and 4-ClC_6H_4 variants giving **23, 25, 27 and 29** with excellent product yield and selectivity in each case (75% to 89% yield, >96:4 er, <5% by-product). The absolute (*R*)-configuration within ester product **23** was unambiguously confirmed by X-ray crystallography, with all other product configurations assigned by analogy. The corresponding 2-naphthyl-substituted variant was insoluble in toluene, and sparingly soluble in $CHCl_3$, so gave reduced conversion to product (~40%) after extended reaction times, giving **31** in 35% yield but excellent enantioselectivity (99:1 er). Further investigations probed the effect of steric hindrance of the C(2)-substituent. It was postulated that equilibration between ring-opened and ring-closed lactols would be perturbed by steric hindrance of the substituent, leading to variation in product distributions upon catalytic acylation. A β-branched C(2)-*i*-Bu substituent led to preferred acyclic by-product formation (65%), but allowed the isolation of **33** in 33% yield and 99:1 er. The effect of a α-branched substitution was probed, with C(2)-cyclopentyl **35** isolated in 15% yield (99:1 er) as the minor product with 73% acyclic product observed. Under the standard reaction conditions, a C(2)-*i*-Pr substituent gave a similar product distribution, giving the preferred formation of the acyclic product in 70% yield and **37** in 15% yield and 99:1 er. In previous work we have shown that use of the selenium catalyst variant (2*S*,3*R*)-HyperSe **16** can lead to enhanced reactivity in tertiary alcohol acylation,[22h] and application of this catalyst (20 mol %) with acetic anhydride as acylating agent gave ester **39** in an improved 40% yield (98:2 er). With C(2)-vinyl and C(2)-phenyl substituents formation of the acylic acylated products was significantly favoured (55% and 93% respectively), with products **41** and **43** isolated in 20% (93:7 er) and 5% (93:7 er) yield. Given the conjugating effect of the aryl substituent, the incorporation of an electron-withdrawing substituent was predicted to bias the product distribution to the cyclic ester product. The use of a C(2)-4-$F_3CC_6H_4$- substituent gave the desired cyclic ester **45** in a much improved 55% yield (92:8 er), while a C(2)-2-pyridyl substituent still gave preferential formation of the acylic product but also **47** in 25% yield (89:11 er).

Further investigations probed the effect of variation within the N(4)-substituent, as well as the incorporation of C(5)- or C(6)-geminal substituents with a C(4)-benzyl substituent as standard. Variation of the N(4)-substituent showed that *N*-Me, *N*-allyl, *N*-phenyl and *N*-PMB were all tolerated well, with in each case <5% of the corresponding diacylated acyclic products observed, giving the desired lactol esters **49, 51, 53 and 55** in 67% to 88% yield and excellent enantioselectivity (up to 99:1 er). The incorporation of geminal substituents at C(5)- or C(6)- was predicted to perturb the rate of equilibration between ring-opened and ring-closed forms, with the Thorpe-Ingold effect expected to give a significant bias towards the cyclic lactol form at equilibrium.[25] Furthermore, geminal substitution at C(5)- or C(6)- was expected to lead to increased substitution in the vicinity of the alcohol in the acyclic ring-opened form thus disfavouring acylation.

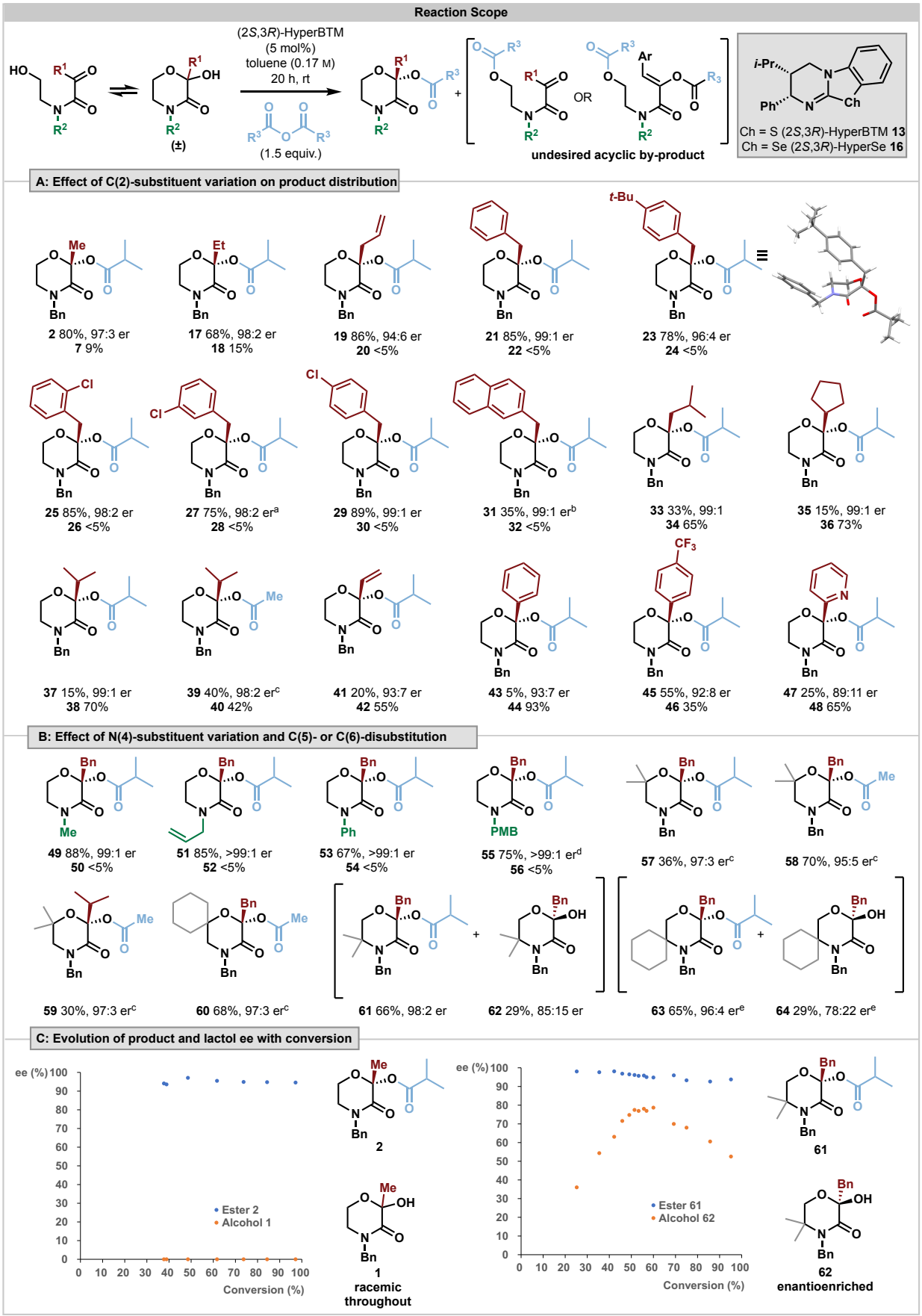


Figure 3: Morpholinone lactol substrate scope. CCDC 2314705 contains the X-ray data for **23**. [a]. Reaction in $CHCl_3$ with 10% mol% (2*S*,3*R*)-HyperSe **16**. [b]. Reaction in $CHCl_3$ and extended to 90 h. [c]. 20 mol% (2*S*,3*R*)-HyperSe **16**. [d]. 10% mol% (2*S*,3*R*)-HyperBTM **13**. [e]. 20% mol% (2*S*,3*R*)-HyperBTM **13**.

In practice, C(6)-disubstitution resulted in <5% product conversion under standard conditions using HyperBTM **13**, necessitating the use of HyperSe **16** (20 mol%) as the Lewis base catalyst. This resulted in exclusive acylation to form the lactol ester **57** in 36% yield (97:3 er) with isobutyric anhydride, while the use of acetic anhydride gave **58** in an improved 70% yield (95:5 er). Similar product distributions were observed with C(2)-*i*-Pr-C(6)-dimethyl substitution, with exclusive formation of lactol ester **59** observed (30%, 97:3 er) using acetic anhydride. Exclusive acylation to give spirocyclic-C(6)-cyclohexyl lactol ester **60** was also observed with acetic anhydride (68%, 97:3 er). In all of these cases, the mass balance of starting materials was made up of the corresponding *racemic* morpholinone lactol, consistent with a DKR process, and the rate of enantiomerization via ring-opening/ring closing being greater than the rate of acylation to give the product.[1v] However, with C(5)-dimethyl- or C(5)-cyclohexyl- substitution, acylation with HyperBTM **13** (5 and 20 mol % respectively) and isobutyric anhydride gave, at ~70% conversion, the desired lactol ester products **61** (66%, 98:2 er) and **63** (65%, 96:4 er) as the exclusive acylated product. In each case the mass balance was made up of the corresponding morpholinone lactol **62** and **64** in *enantioenriched* form (85:15 and 78:22 er respectively). Intrigued by the observation of enantioenriched remaining lactol with C(5)-substitution in these DKR processes, temporal reaction monitoring was undertaken to probe the evolution of product ester and lactol ee with reaction conversion (Figure 3C). Notably, using lactol **1** the ee of the lactol esters **2** remained high independent of reaction conversion, with the corresponding lactol **1** racemic throughout. This is consistent with the rate of enantiomerization (by ring-opening and ring closure) being significantly faster than lactol acylation. However, with C(5)-dimethyl substitution, while the lactol ester **61** is formed in high enantioselectivity throughout, the unreacted alcohol **62** is enantioenriched, reaching a maximum er value of 90:10 at ~60% conversion. Notably, in this acylation conversion to lactol ester 61 reached ~50% conversion within 5 hours, with >95% conversion only achieved with extended reaction times (72 hours). This is consistent with a slow rate of enantiomerization by ring-opening and ring-closure compared to acylation, presumably reflecting the expected Thorpe-Ingold effect of the C(5)-dimethyl substituents.

Further work considered the propensity for DKR in the related benzoxazinone scaffold (Figure 4), with benzannulation expected to significantly change both the reactive conformation and relative rates of competitive acylation of the ring-opened phenol or the tetra-substituted lactol.[23e] Optimisation using the C(2)-phenyl substituted lactol (see SI for full details) showed that chlorinated solvents ($CHCl_3$ and CH_2Cl_2) led to significant (up to 50%) formation of the unwanted ring-opened ester product. Toluene led to essentially exclusive formation of the benzoxazinone lactol ester, while the use of diphenylacetic anhydride and the addition of base was necessary to promote full conversion, giving **66** in 86% yield and 92:8 er. Reaction monitoring showed that the lactol remained racemic and the enantioselectivity of the lactol ester remained constant with conversion (see SI), consistent with the rate of enantiomerization being faster than acylation in this system. Subsequent variation of the C(2)-substituent showed that benzyl, methyl, vinyl and allyl substituents were tolerated, alongside N(4)-Me substitution, giving the corresponding lactols **67**-**71** in up to 88% yield and 91:9 er. The effect of substitution of the benzoxazinone skeleton was also probed, with C(6)- and C(8)-substituted derivatives giving **73**-**75** in good to excellent yield and up to 90:10 er. Notably, the incorporation of a C(7)-F substituent gave preferential formation of the ring-opened ester (63% yield) but gave **72** in 23% yield (90:10 er).

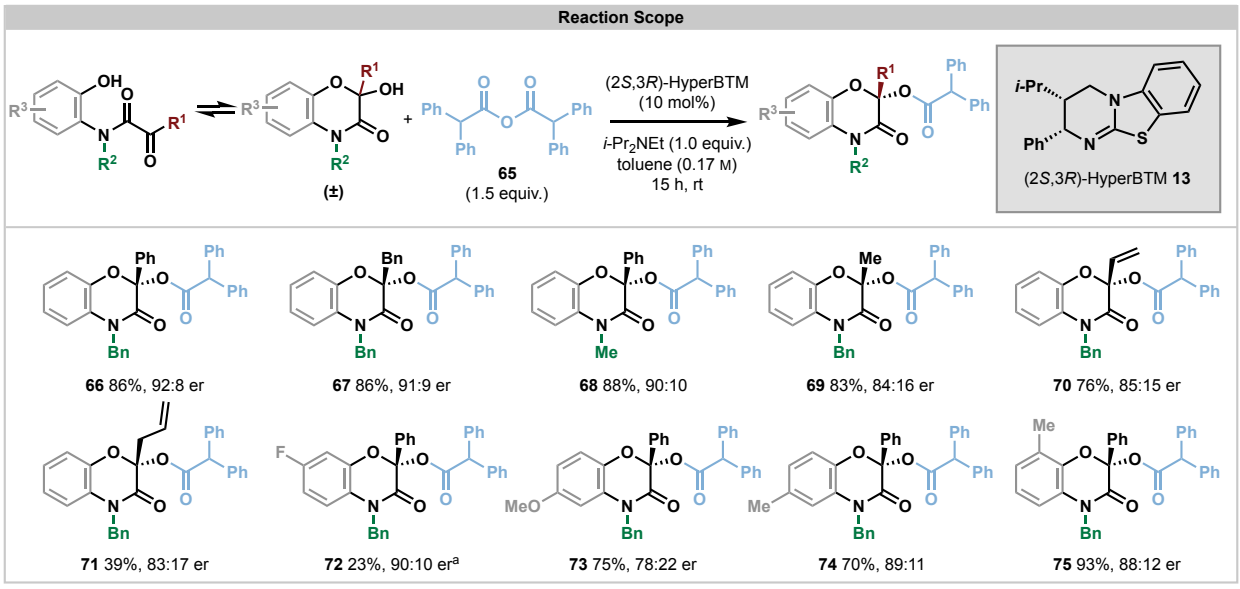


Figure 4: Benzoxazinone Lactol substrate scope. [a]. 63% ring-opening ester isolated.

Density Functional Theory (DFT) was used to identify the factors that determine the preferences behind cyclic vs acyclic products and enantioselectivity of the acylation. Specifically, PBE level of theory with Grimme's empirical dispersion corrections with Becke Johnson dampening parameter (D3BJ) and the 6-31G(d) basis set was used. All computations were performed under SMD solvation with toluene at 298.15 K.[26] The energies were refined with the larger def2-TZVP basis set.[27] Recognised enantiorecognition motifs in isothiourea-catalyzed KRs include aryl,[28] heteroaryl,[29] alkenyl,[28d] alkynyl,[28a] heteroatom, C=O,[30] CF_2,[31] and P=O substituents.[32] With potentially competitive N-C=O and heteroatom O structural motifs adjacent to the carbinol within the morpholine lactol skeleton in this case, the origins of

the observed enantioselectivity in this DKR process were investigated using DFT.

The (2*S*,3*R*)-HyperBTM **13** catalyzed acylation of C(2)-Me substituted morpholinone lactol **1** by isobutyric anhydride was investigated (Figure 5). As reaction monitoring of this system (Fig **3c**) had indicated that the lactol is racemic throughout, the barrier to enantiomerisation via reversible ring opening and closure was expected to be small compared to alcohol acylation, and this was confirmed by DFT (See Supporting Information). Following the model developed in our previous kinetic resolution work,[33] enantiorecognition between an acylated HyperBTM isothiouronium intermediate with the enantiomers of the morpholinone lactol **1**, as well as acylation of the ring-opened alcohol **76** was probed. In all transition structures, two common structural motifs were seen: i. an O•••S chalcogen bonding (n_O to $\sigma^*_{S\text{-}C}$) interaction was observed between the acyl oxygen and the catalyst sulfur.[26-33] ii. the isobutyrate deprotonating the alcohol participated in non-classical H-bonding to the acylated catalyst +NC-H substituent (2.1–2.3 Å).[22g, 34]

The major morpholinone (*S*)-lactol **1** acylation transition state **TS-II** leads to the observed major cyclic (*R*)-ester product **2** with a barrier of 13.7 kcal/mol (*note: CIP priority changes*). The acylation **TS-I** gives the minor acyclic ester product **7** with a barrier of 15.6 kcal/mol. This is 1.9 kcal/mol higher than the favoured **TS-II** leading to the cyclic ester product **2** (96:4). This result is in line with the observed product ratios of 91:9 (Figure 5A).

To understand why acylation of lactol **1** was favoured over acyclic alcohol **76**, their ground states were evaluated (Figure 5B). The cyclic lactol **1** was thermodynamically favoured by 1.3 kcal/mol, and the interconversion between them was rapid compared to the acylation process ($\Delta G^{\ddagger}$ = 11.7 kcal/mol, ~3–4 kcal/mol lower) – i.e. a Curtin-Hammett scenario is operative. Thus the barriers of **TS-I** and **TS-II** determine the cyclic vs acyclic preference ($\Delta G^{\ddagger}$ = 13.7 and 15.6 kcal/mol, respectively), not the thermodynamic stability of the starting materials **1** and **76**. The favoured **TS-II** possessed a stabilizing interaction between the acyl isothiouronium ion and the more Lewis basic lactol N-C=O carbonyl donor (C•••O=C = 2.83 Å, interaction highlighted in green). In comparison, in the disfavoured acyclic alcohol acylation **TS-I**, the isothiouronium and carbonyl are much further apart (C•••O=C = 4.05 Å, interaction highlighted in grey), resulting in a weaker interaction (Figure 5C).[20a, 35] Consistent with this hypothesis, the Wiberg bond index of this interaction in **TS-II** was 0.0102, suggesting significantly greater bonding interaction compared to that of **TS-I** (0.0006).[36]

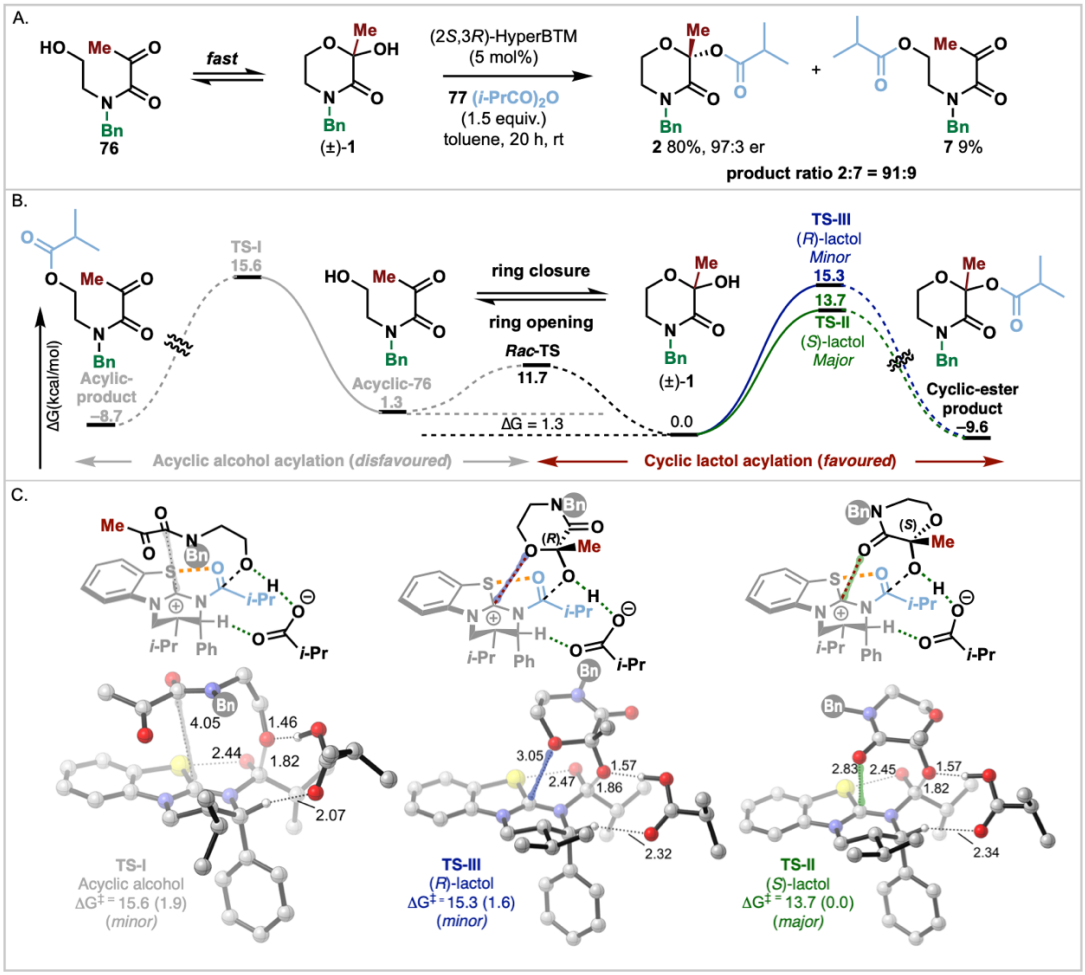


Figure 5: A. Experimental conditions and product distributions. B. DFT computed bidirectional reaction profile of acylation of C(2)-Me substituted enantiomeric morpholinone lactol **1** and acyclic alcohol **76**. C. DFT computed acylation transition structures. For clarity, non-essential hydrogens and N-benzyl groups are not shown. Full structures are shown in Supporting Information. The location of the N-benzyl substituents are highlighted in grey. Energies in kcal/mol, distances in Å.

The origins of enantiodiscrimination in the acylation of cyclic ester products were also investigated (Figure 5C). Acylation of the (*R*)-lactol via **TS-III** had a barrier of 15.3 kcal/mol that leads to the minor (*S*)-ester product **2**. This barrier was 1.6 kcal/mol higher than **TS-II** (94:6 er), which is in good agreement with experiment (97:3 er). The key interactions responsible for the observed enantiodiscrimination are shown in Fig 3, bottom. In the disfavoured **TS-III**, the isothiouronium interacts with the less Lewis basic lactol ether O (C•••OC = 3.05 Å, interaction highlighted in blue). This contrasts with the favoured **TS-II**, where the more Lewis basic lactol N-C=O carbonyl donor participates (C•••O=C = 4.05 Å, interaction highlighted in grey).

In conclusion, a highly enantioselective isothiourea-catalysed acylative DKR of tetra-substituted morpholinone and benzoxazinone-derived lactols has been developed. High enantioselectivity and good to excellent product yields (up to 88%, 99:1 er) are observed across a broad range of substrate derivatives incorporating substitution at N-(4) and C(2), di- and spirocyclic substitution at C(5)- and C(6)-, as well as benzannulation. The factors leading to high selectivity in this DKR process have been probed through computation, with an N-C=O •••isothiouronium interaction identified as key to producing lactol ester products with high enantioselectivity. Ongoing work from within our laboratory is aimed at developing further effective DKR processes using isothioureas as catalysts and its broad application to heterocycle synthesis.

Supporting Information ((optional))

The authors have cited additional references within the Supporting Information.[37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54], [55], [56], [57], [58], [59], [60]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The research data supporting this publication can be accessed from "Isothiourea-Catalysed Acylative Dynamic Kinetic Resolution of Tetra-substituted Morpholinone and Benzoxazinone Lactols". Pure ID: 298523118. University of St Andrews Research Portal. https://doi.org/10.17630/be31964f-f256-4aeb-92cc-5598add7e635

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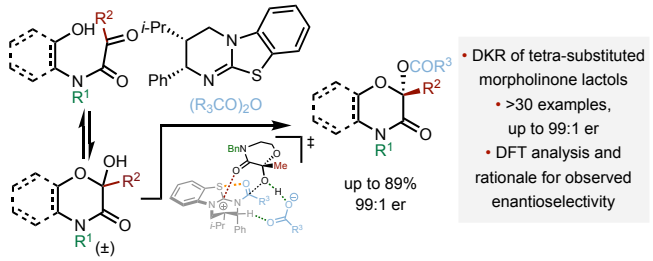

A highly enantioselective isothiourea-catalysed acylative DKR of tetra-substituted morpholinone and benzoxazinone-derived lactols is reported. DFT studies identify an N-C=O•••isothiouronium interaction as key to producing products in highly enantioenriched form.

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