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Enantioselective Catalysis

Synthesis of Tetra-Substituted 3-Hydroxyphthalide Esters by Isothiourea-Catalysed Acylative Dynamic Kinetic Resolution

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Abstract: A general and highly enantioselective method for the preparation of tetra-substituted 3-hydroxyphthalide esters via isothiourea-catalysed acylative dynamic kinetic resolution (DKR) is reported. Using (2*S*,3*R*)-HyperBTM (5 mol %) as the catalyst, the scope and limitations of this methodology have been extensively probed, with high enantioselectivity and good to excellent yields observed (>40 examples, up to 99 %, 99:1 er). Substitution of the aromatic core within the 3-hydroxyphthalide skeleton, as well as aliphatic and aromatic substitution at C(3), is readily tolerated. A diverse range of anhydrides, including those from bioactive and pharmaceutically relevant acids, can also be used. The high enantioselectivity observed in this DKR process has been probed computationally, with a key substrate heteroatom donor O···acyl-isothiouronium interaction identified through DFT analysis as necessary for enantiodiscrimination.

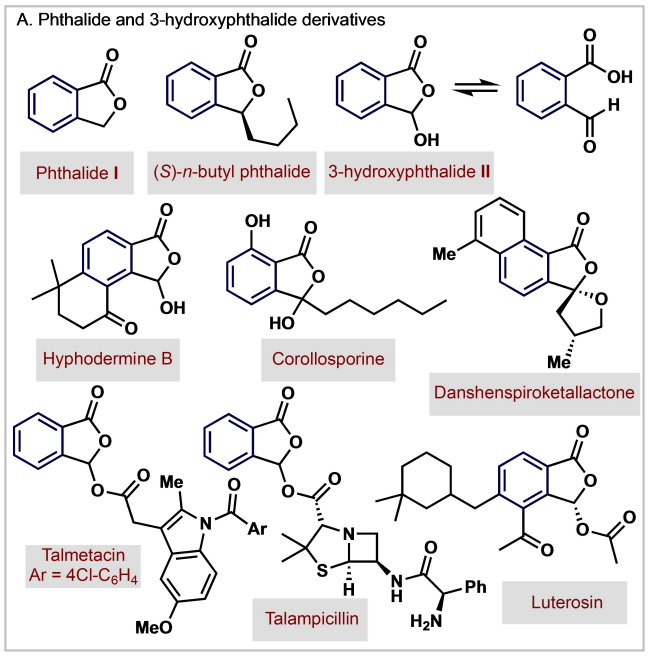

Figure 1. Importance of 3-hydroxyphthalides and their ester derivatives

Introduction

The bicyclic 3*H*-isobenzofuran-1-one skeleton, commonly known as the phthalide scaffold **I**, is characterized by the fusion of a γ-lactone with a benzene core (Figure 1A). A range of compounds bearing the phthalide structure are found within natural products and are known to have significant and varied biological activities.[1] For example, *n*-butyl phthalide is marketed as an anti-platelet drug, with the (*S*)-enantiomer more effective than its enantiomer.[2] Phthalide, and in particular its 3-substituted derivatives, are also widely recognised as valuable starting materials in organic synthesis, and have been particularly used for the synthesis of naphthalene and naphthacene natural products.[1a] 3-Hydroxyphthalide **II** reversibly ring-opens to generate 2-formylbenzoic acid, with the cyclised form favoured in most solvents.[1f] A range of 3-hydroxyphthalides are natural products and possess significant bioactivity. For example, hyphodermin B contains a C(3)-hydroxyl substituent,[3] while tetra-substituted 3-hydroxyphthalide natural products such as Corollosporine[3b] and Danshenspiroketallactone[4] also show biological activity (Figure 1A). Significantly, 3-hydroxyphthalide ester derivatives are also of widespread interest.[1a,5] For example, Luterosin is a natural product that displays ichthyotoxic activity,[6] while ester derivatives of 3-hydroxyphthalide have been widely investigated as prodrugs[7] of the corresponding carboxylic acid. In this area, marketed prodrugs of acylated 3-hydroxyphthalide compounds such as Talmetacin[8] and Talampicillin[1e,9] have been described. Given their significance, catalytic methods capable of preparing enantiopure tri-substituted 3-hydroxyphthalide esters have been investigated,[10] although methods that allow the effective preparation of the corresponding tetra-substituted phthalide ester analogues are a recognised synthetic challenge.

Within this area the configurational lability of the 3-hydroxyphthalide unit[1a,f] (through ring-opening and ring-

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closure) has been exploited as a key testing ground for the development of dynamic kinetic resolution (DKR) processes (Figure 2A).[11,12] The current state-of-the-art in this area has been described by Chi and co-workers,[13a] who demonstrated an oxidative NHC catalysed enantioselective acylative DKR of 3-hydroxyphthalides with excellent enantioselectivity (up to 98:2 er) although a stoichiometric oxidant (3,3′,5,5′-tetra-*tert*-butyldiphenoquinone, DQ) is required. Further work by Zhang and co-workers[13b] demonstrated the use of imidazole derivative Cy-DPI **2** in the DKR of 3-hydroxyphthalide derivatives, generating ester products with excellent enantioselectivity (up to >99:1 er). The widely recognized remaining challenge in the area of acylative DKR is to develop effective processes for the preparation of enantioenriched tetra-substituted ester analogues from lactols. In the preceding manuscript[14] the isothiourea[15] (2*S*,3*R*)-HyperBTM was shown to promote the DKR of tetra-substituted morpholinone and benzoxazinone lactols to generate the corresponding lactol esters in highly enantioenriched form. In this manuscript (Figure 2B), the application of isothiourea-mediated enantioselective acylative DKR[16] to tetra-substituted 3-hydroxyphthalide derivatives is reported. The scope and limitations of this methodology have been extensively probed, with high enantioselectivity and good to excellent yields (up to 99% yield, 99:1 er) observed across a broad range of substrate derivatives. To the best of our knowledge, the only previous examples of such a protocol were demonstrated as part of Chi's work,[13a] elegantly showing the feasibility of this process but with only moderate to good enantioselectivity observed (up to 98:2 er, 7 examples). During the peer-review of this manuscript a bifunctional organocatalyst catalysed enantioselective acylation of perfluorinated tetra-substituted phthalides was reported.[17]

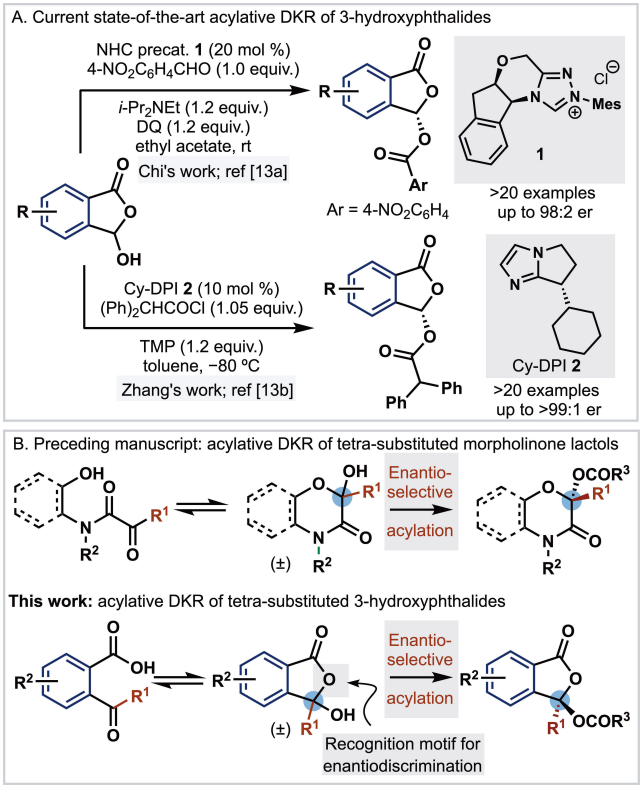


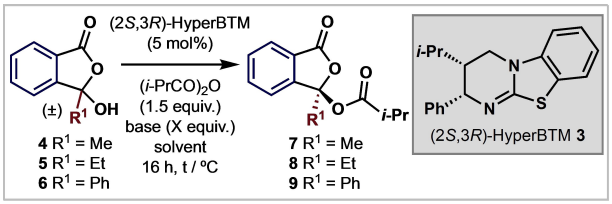
Figure 2. A. State-of-the-art DKR approaches to enantioenriched tri-substituted 3-hydroxyphthalide esters. B. This work.

Results and Discussion

Optimisation

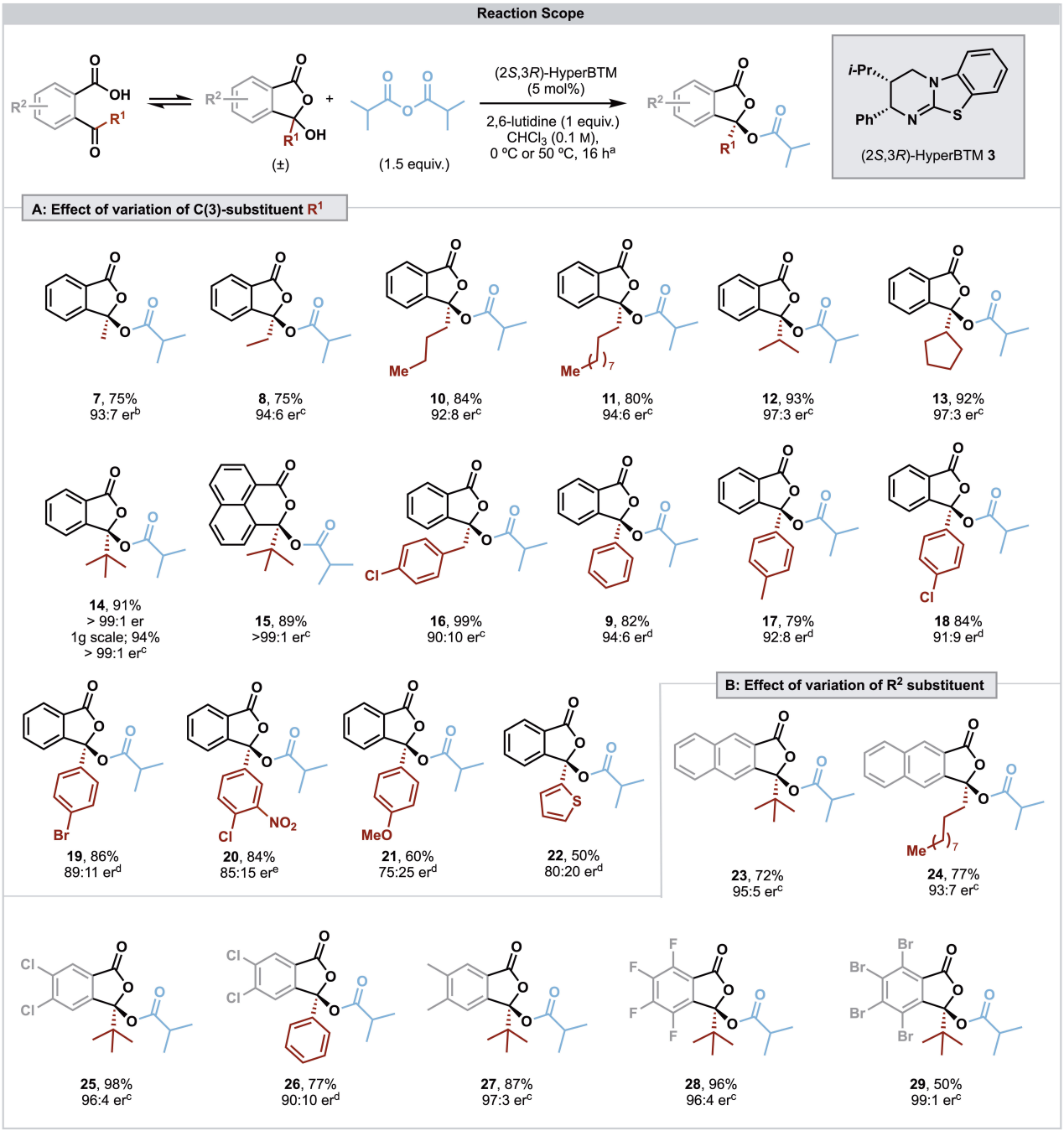
The proposed DKR process was initially developed using the acylation of 3-methyl-3-hydroxyphthalide **4** as a model substrate to generate the corresponding tetra-substituted ester (Table 1). Treatment of **4** with the isothiourea (2*S*,3*R*)-HyperBTM **3** (5 mol %), isobutyric anhydride (1.5 equiv.), *i*-Pr_2NEt (1.5 equiv.) in toluene gave a 57% yield of **7** in 65:35 er (entry 1). Variation of the solvent showed that higher enantioselectivity was observed in chlorinated solvents (CH_2Cl_2 or $CHCl_3$), giving **7** in 88% yield and 83:17 er (entries 3–4). Variation of the base equivalents showed that the base was necessary for optimal reactivity, although the stoichiometry could be reduced (to 1.0 equiv.) without detriment to product yield or selectivity (entries 4–6). Alternative bases (lutidine and K_2CO_3) showed marginally improved enantioselectivity at room temperature (entries 7 and 8), with −20 °C proving optimal, giving ester **7** in 73% isolated yield and 93:7 er (entries 9 and 10). Using isobutyric anhydride as the acyl donor gave higher product yield and enantioselectivity than in situ activation[20g–o] of the

Table 1: [a]. Product yield calculated from ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard; brackets indicate isolated yield. [b]. measured by HPLC analysis on a chiral stationary phase.



Entry	R^1	base (equiv.)	Solvent (0.1 m)	T/°C	Yield[a]	er[b]
1	Me (**4**)	*i*-Pr_2NEt (1.5)	toluene	rt	57	65:35
2	Me (**4**)	*i*-Pr_2NEt (1.5)	MeCN	rt	66	62:38
3	Me (**4**)	*i*-Pr_2NEt (1.5)	CH_2Cl_2	rt	81	80:20
4	Me (**4**)	*i*-Pr_2NEt (1.5)	$CHCl_3$	rt	88	83:17
5	Me (**4**)	*i*-Pr_2NEt (1.0)	$CHCl_3$	rt	85	85:15
6	Me (**4**)	–	$CHCl_3$	rt	18	88:12
7	Me (**4**)	K_2CO_3 (1.0)	$CHCl_3$	rt	80	85:15
8	Me (**4**)	Lutidine (1.0)	$CHCl_3$	rt	81	87:13
9	Me (**4**)	Lutidine (1.0)	$CHCl_3$	0	58	90:10
10	Me (**4**)	K_2CO_3 (1.0)	$CHCl_3$	−20	93 (75)	93:7
11	Et (**5**)	Lutidine (1.0)	$CHCl_3$	rt	77	92:8
12	Et (**5**)	Lutidine (1.0)	$CHCl_3$	0	75 (70)	94:6
13	Ph (**6**)	Lutidine (1.0)	$CHCl_3$	rt	44	94:6
14	Ph (**6**)	Lutidine (1.0)	$CHCl_3$	50	86 (82)	94:6

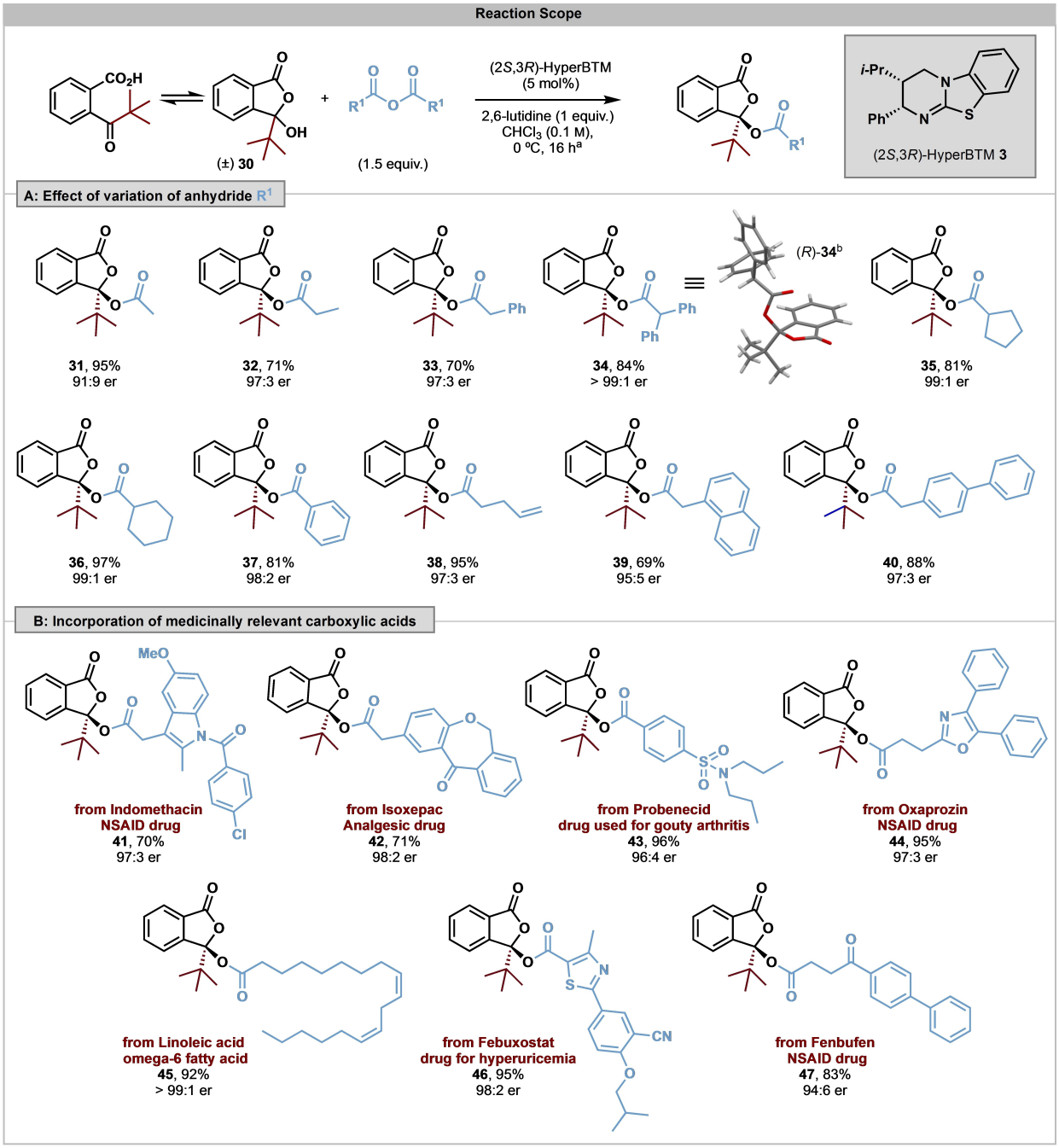
corresponding acid (see Supporting Information for further details). Application of these conditions to alternative substrates (R=Et (±)-**5**, Ph (±)-**6**) indicated that the nature of the C(3)-substituent at the carbinol centre has a profound impact upon both rate of product formation and product enantioselectivity (~20 % conversion at −20 °C, see Supporting Information for details). For example, incorporation of a C(3)-ethyl substituent resulted in improved yield and selectivity compared to the C(3)-methyl substituted derivative at rt or 0 °C (entries 11 and 12), giving ester **8** in 70 % yield and 94 : 6 er. Introducing a C(3)-Ph substituent at the carbinol centre **6** resulted in moderate yield but high enantioselectivity at rt (entry 13). Increasing the reaction temperature to 50 °C gave improved conversion while maintaining enantioselectivity, giving **9** in 82 % yield and 94 : 6 er (entry 14).



Scheme 1. [a]. Reaction conditions: substrate (0.4 mmol), isobutyric anhydride (0.6 mmol), (2*S*,3*R*)-HyperBTM (0.02 mmol), 2,6-lutidine (0.4 mmol), and $CHCl_3$ (0.1 M), 16 h. Er value measured by HPLC analysis on a chiral stationary phase. Yield represents the isolated yield. [b]. reaction conducted at −20 °C using K_2CO_3 as a base. [c]. reaction carried out at 0 °C to generate **8**,**10**–**16**, **23**–**25**, **27**–**29**. [d]. reaction carried out at 50 °C to generate **9**, **17**–**19**, **21**–**22** and **26**. [e]. reaction conducted at rt to generate **20**.

Scope and Limitations

With proof-of-principle for this strategy demonstrated, the scope and limitations of the developed process was investigated (Scheme 1). Variation of the steric and electronic properties of the C(3)-substituent within the phthalide scaffold was initially varied (Scheme 1A). With aliphatic C(3)-substituents reaction at 0 °C showed that progressive variation of the linear carbon chain from C(3)-methyl to C(3)-ethyl, C(3)-*n*-butyl and C(3)-*n*-decyl was tolerated, giving esters **7**, **8**, **10** and **11** in excellent product yield and enantioselectivity (75 % to 84 % yield, up to 94:6 er). The incorporation of C(3)-α-branched substitution within the substrate was developed, with both C(3)-*i*-Pr and C(3)-cyclopentyl substitution tolerated, giving **12** and **13** respectively in excellent yield (>90 %) and 97:3 er. To further test the effect of steric hindrance the DKR of the corresponding C(3)-*t*-butyl variant was probed, giving ester **14** in 91 % yield



Scheme 2. [a]. Reaction conditions: **30** (0.2–0.4 mmol), anhydride (0.3–0.6 mmol), (2*S*,3*R*)-HyperBTM (0.01–0.02 mmol), 2,6-lutidine (0.2–0.4 mmol), and $CHCl_3$ (0.1 M), 16 h. Er value measured by HPLC analysis on a chiral stationary phase. Yield represents the isolated yield after chromatographic purification. [b]. CCDC 2312680 (**34**) contain the supplementary crystallographic data for this paper.

and >99:1 er. Intrigued by the effectiveness of this protocol, further extension to a C(3)-*t*-butyl-isochromenone derivative was tested, giving **15** in 89% yield and >99:1 er. A C(3)-benzyl substituent gave excellent product yield and high enantioselectivity **16** (99%, 90:10 er). A variety of C(3)-aryl substituted derivatives were tested under the DKR protocol. Notably while all C(3)-alkyl derivatives prefer the cyclized form, all C(3)-aryl analogues exist predominantly in their ring-opened form, presumably reflecting the conjugation between the ketone carbonyl and the (hetero)aromatic ring system. Acylative DKR was therefore carried out at 50 °C, with C(3)-Ph, C(3)-4-MeC_6H_4, C(3)-4-ClC_6H_4, C(3)-4-BrC_6H_4 and C(3)-4-Cl,3-$NO_2C_6H_3$ substitution giving the corresponding esters **9**, **17**–**20** in 79% to 86% yield and 85:15 to 94:6 er. C(3)-4-MeOC_6H_4 and C(3)-2-thiophene derivatives also generated the corresponding esters **21** and **22** under these conditions, but gave reduced product yields and enantioselectivity and so represent a limitation of this protocol. We speculate that the variation in enantioselectivity with C(3)-aryl substitution is due to disruption of the non-covalent interactions that govern the molecular enantiorecognition event. Further investigations probed the effect of variation within the aromatic phthalide core (Scheme 1B). Incorporation of naphthyl-substitution was tolerated, with C(3)-*t*-butyl and C(3)-*n*-decyl substitution giving the corresponding ester derivatives **23** and **24** in 72% yield (95:5 er) and 77% yield (93:7 er) respectively. The incorporation of 5,6-dichloro- and 5,6-dimethyl substitution was tolerated, alongside perfluoro- and perbromo-substitution, giving the corresponding esters **25**–**29** in good to excellent yield and up to 99:1 er.

Given the recognized utility of 3-hydroxyphthalidyl esters as natural products and prodrugs, further studies probed the effect of variation of the anhydride reactant, aiming to develop a general method to prepare a range of tetra-substituted phthalidyl esters (Scheme 2A). Using (±)-C(3)-*t*-butyl-3-hydroxyphthalide (**30**) as standard, variation of the anhydride component was developed. Using acetic, propionic and phenylacetic anhydride gave the corresponding esters in 70 to 95% yield and excellent enantioselectivity (**31**–**33**, up to 97:3 er). The use of α-branched anhydrides gave the corresponding esters with exceptional levels of enantiocontrol, with diphenylacetic anhydride, cyclopentane- and cyclohexane carboxylic anhydride giving the corresponding esters **34**, **35** and **36** in excellent yields and 99:1 er. The absolute (*R*)-configuration within ester product **34** was unambiguously confirmed by X-ray crystallography, with all other product configurations assigned by analogy. Benzoic anhydride, pent-4-enoic anhydride, 1-naphthylacetic anhydride as well as 4-Ph-phenylacetic anhydride were all tolerated, giving esters **37**–**40** in ≥95:5 er. Further work sought to challenge the isothiourea catalyst (2*S*,3*R*)-HyperBTM **3** in this protocol through the incorporation of medicinally relevant carboxylic acid motifs within the tetra-substituted phthalidyl ester products. A range of anhydrides of commercially available drugs and natural products were generated and subjected to this DKR process (Scheme 2B).

As an initial target, the phthalidyl ester product **41** derived from Indomethacin was targeted, as this would generate an enantioenriched tetra-substituted C(3)-*t*-Bu analogue of the known prodrug Talmetacin. Treatment of (±)-**30** under these standard reaction conditions gave the desired product ester **41** in 70% yield and 97:3 er. The generality of this approach was then examplified, with the tetra-substituted phthalidyl ester products **42**–**47** derived from Isoxepac, Probenecid, Oxaprozin, linoleic acid, Febuxostat and Fenbuprofen respectively all generated in excellent yields and in ≥94:6 er, clearly demonstrating the functional group tolerance of this methodology.

A simplified generic mechanistic Scheme for this acylative DKR process is shown in Figure 3. Acylation of (2*S*,3*R*)-HyperBTM **3** with isobutyric anhydride generates an intermediate acyl isothiouronium ion pair. This reacts in the enantiodetermining step preferentially with the (*R*)-enantiomer of the substrate (**4** R=Me, **30** R=*t*-Bu) to generate the enantioenriched phthalide ester (**7** R=Me, **14** R=*t*-Bu) and an isothiouronium carboxylate ion pair. Subsequent reaction with the 2,6-lutidine generates the free HyperBTM catalyst. Reversible ring-opening and closure of the 3-hydroxyphthalide to the corresponding keto-acid is postulated to be fast with respect to acylation of either substrate enantiomer, resulting in substrate enantiomerization[18] and facilitating a DKR.

Consistent with this model, reaction monitoring of the acylative DKR of substrate (±)-**30** (R=*t*-Bu) showed that the enantioselectivity of product (*R*)-ester (99:1 er) was consistent throughout the reaction (see Supporting Information for further information). The enantiomers of phthalide **30** could not be resolved satisfactorily by HPLC analysis and so its enantioselectivity could not be unambiguously deter-

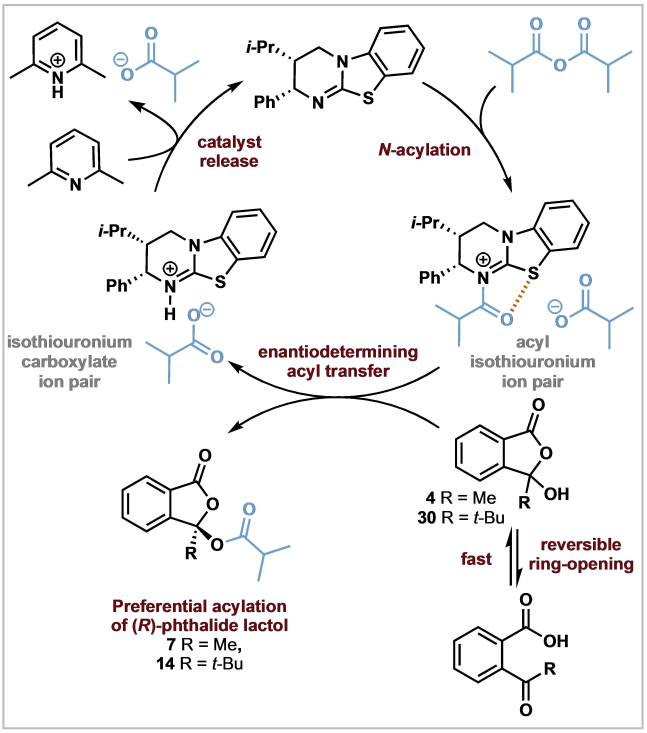


Figure 3. General mechanistic scheme for the observed acylative DKR.

mined. However, modelling using the DYNRES simulator developed by Faber and co-workers[19] allowed an estimate of the relative rates of enantiomerization, (*R*)-substrate reaction, and (*S*)-substrate reaction as >100:100:1 (see SI).

To uncover the structural factors leading to the high enantioselectivity observed in this DKR, the interplay between potential aryl and heteroatom-O enantiorecognition motifs[20a–h] within the antipodes of the 3-hydroxyphthalide derivatives **4** (R^1=Me) and **30** (R^1=*t*-Bu), and their interaction with an *N*-acylated HyperBTM-derived isothiouronium intermediate, were probed computationally. Computations were carried out at the M06-2X$_{PCM(chloroform)}$/def2-TZVP//M06-2X$_{PCM(chloroform)}$/def2-SVP level of theory using Gaussian16.[21] Building upon previous work,[22] an O···S chalcogen bonding (n_O to σ^*_{S-C})[24–31] interaction acts as a conformational lock within the acylated HyperBTM intermediate, while the isobutyrate counterion deprotonates the alcohol and engages in a non-classical H-bond to the

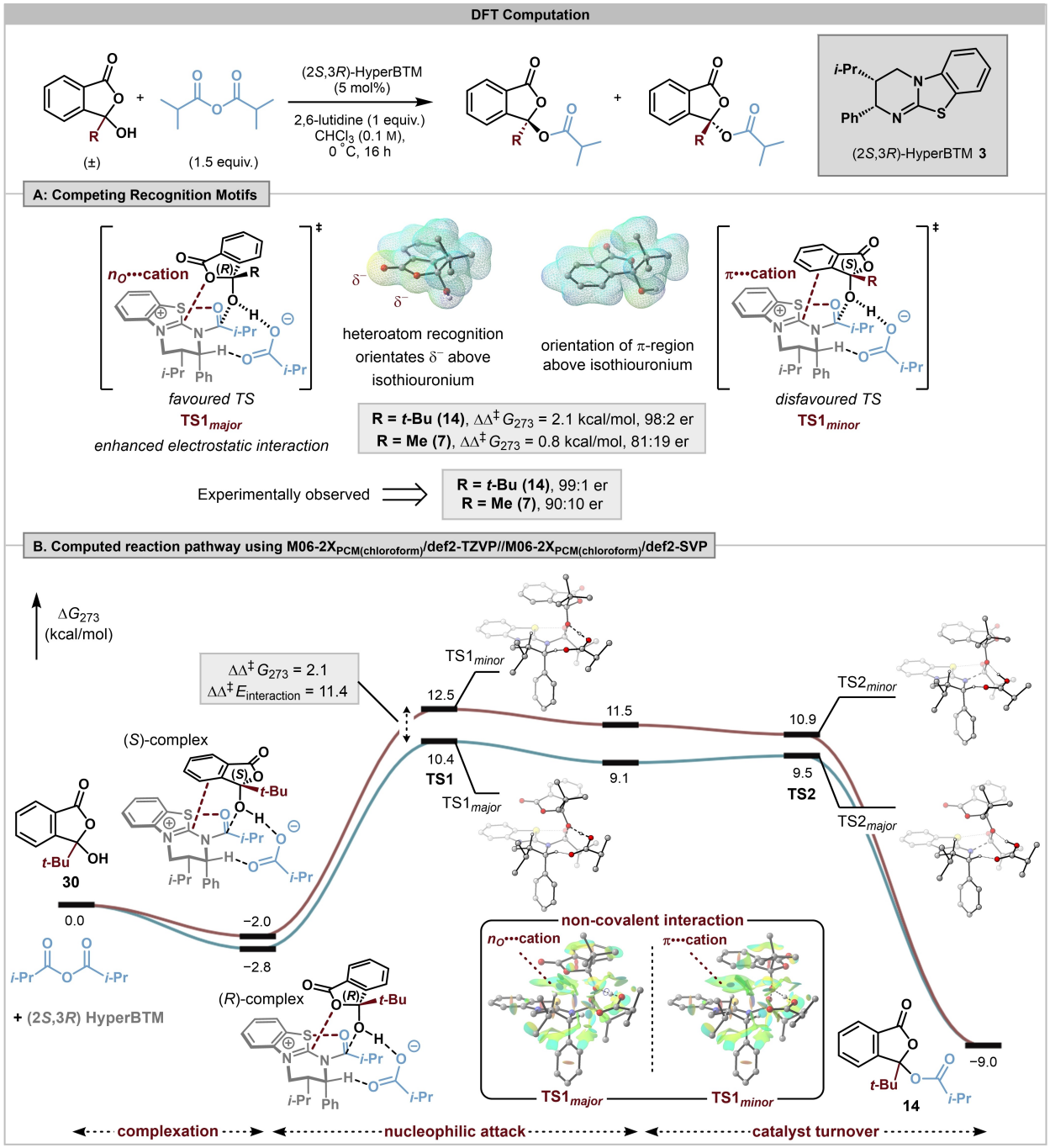


Figure 4. Computational studies of the DKR process. A. Competition of recognition motifs. Electrostatic potential maps generated with an isosurface of 0.2 and a colour scale from −0.2 a.u. (red) to +0.2 a.u. (blue). B. Reaction profile for the DKR to form **14** following reference.[22] ΔG_{273} at the level of M06-2X$_{PCM(chloroform)}$/def2-TZVP//M06-2X$_{PCM(chloroform)}$/def2-SVP in kcal/mol.

acylated catalyst +NC–H substituent.[23] To deliver high enantioselectivity, a donor substrate motif is needed to promote enantiorecognition through interaction with the positively charged acylated isothiouronium intermediate.[20a–h] Competitive transition states arising from stabilisation of the acylated isothiouronium intermediate with either the (*R*)-lactol utilising the O-heteroatom adjacent to the carbinol, or with the (*S*)-lactol from the benzannulated aryl substituent, were calculated to understand the high product enantioselectivity observed (Figure 4A).

For substrate **30** (R = *t*-Bu) a difference in free energy of the key stereodetermining transition states (TS1) arising from acylation of the (*R*)- and (*S*)-substrate enantiomers of 2.1 kcal/mol is calculated, reflecting a predicted 98:2 er, consistent with the 99:1 er observed experimentally (Figure 4B). In the favoured pathway using the (*R*)-substrate enantiomer, the O-heteroatom within the lactone interacts with the isothiouronium intermediate, whereas in the (*S*)-pathway, the aryl ring is orientated above the catalyst, instead exhibiting a cation-π type stabilising interaction. This preference is consistent with previous observations where an N–C=O carbonyl donor is the preferred recognition motif compared to an aromatic group in isothiourea catalysed acylation. After the stereodetermining transition state, a shallow tetrahedral intermediate is formed, prior to a vanishingly small transition state governing the release of the catalyst (TS2).

Non-covalent interaction (NCI) plots visually indicate favourable interactions within the system, with both diastereomeric transition states showing stabilising (green) interactions with the isothiouronium intermediate (inset in Figure 4B). Both electron rich motifs form stabilising interactions with the *N*-acylated catalyst; however, by considering the stabilisation of the complex relative to the three isolated components of TS1 (see SI), we can quantify the interaction for each recognition motif. O heteroatom recognition in $TS1_{major}$ is favoured by 11.4 kcal/mol relative to the aryl recognition in $TS1_{minor}$ which is a strong contributor towards the selectivity. This arises from the preferential orientation of the N-C=O carbonyl donor motif over the isothiouronium ion that can be observed from the electrostatic potential surface in Figure 4A.

As expected, variation of the **R** group indicated that the size of this substituent can have an influence on the selectivity, with a computed reduction in selectivity for the formation of ester **7** from **4** (**R**=Me) to 81:19 er ($\Delta\Delta^{\ddagger}G_{273}$ = 0.8 kcal/mol) which is qualitatively in line with the experimentally observed enantioselectivity of 90:10 er at 0 °C.

In conclusion, a highly enantioselective isothiourea-catalysed acylative DKR of tetra-substituted 3-hydroxyphthalide derivatives is reported using (2*S*,3*R*)-HyperBTM (5 mol %) as the catalyst (> 40 examples in total). The scope and limitations of this methodology have been extensively probed, with high enantioselectivity and good to excellent yields (up to 99 %, 99:1 er) observed across a broad range of substrate derivatives. Aliphatic and aromatic substitution is tolerated at C(3), as well as substitution of the aromatic core. A diverse range of anhydrides, including those derived from bioactive and pharmaceutically relevant acids, can be used as the acyl donor in this catalytic process, allowing the preparation of a tetra-substituted C(3)-*t*-Bu analogue of the known prodrug Talmetacin in 97:3 er. The high enantioselectivity observed in this DKR process has been rationalised through DFT computation, with a heteroatom O···isothiouronium interaction identified as being key to high enantiodiscrimination in this process. Ongoing work from within our laboratory is aimed at developing further effective DKR processes using isothioureas as catalysts alongside developing an understanding of alternative recognition motifs that can give rise to enantioselectivity in such processes.

Supporting Information

The authors have cited additional references within the Supporting Information.[32–52]

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The research data supporting this publication can be accessed from "Enantioselective Synthesis of Tetra-substituted 3-Hydroxyphthalide Esters by Isothiourea-Catalysed Acylative Dynamic Kinetic Resolution". Pure ID: 298501779. University of St Andrews Research Portal. https://doi.org/10.17630/61bd37fd-52fe-4d37-bb5d-d2502fd2d0b9.

Keywords: isothiourea · dynamic kinetic resolution · tetra-substituted 3-hydroxyphthalide ester · acylation · enantioselective

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