# Enantioselective 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 computation, with a key substrate heteroatom donor O•••acyl-isothiouronium interaction identified through DFT analysis as necessary for enantiodiscrimination.

**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.

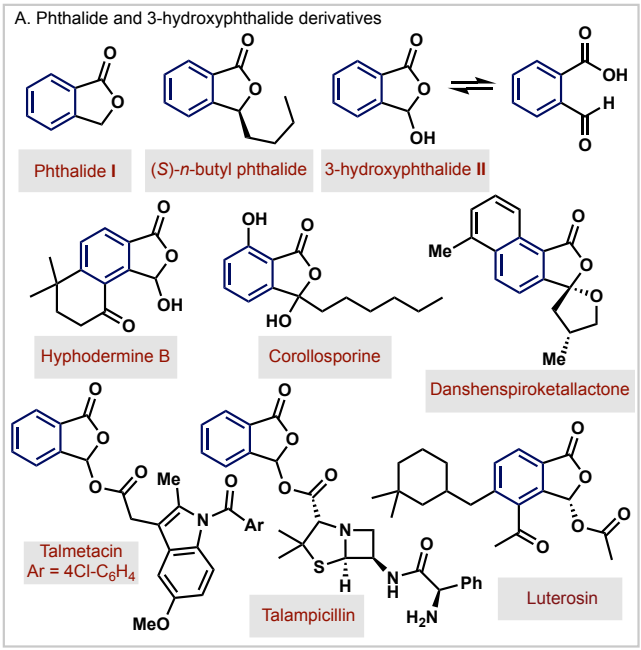



**Figure 1:** The phthalide skeleton and the importance of 3-hydroxyphthalide a and their ester derivatives

Within this area the configurational lability of the 3-hydroxyphthalide unit[1a, 1f] (through ring-opening and ring-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,[13] 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[14] 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 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,[5] elegantly demonstrating the feasibility of this process but with only moderate to good enantioselectivity observed (up to 86:14 er, 7 examples).

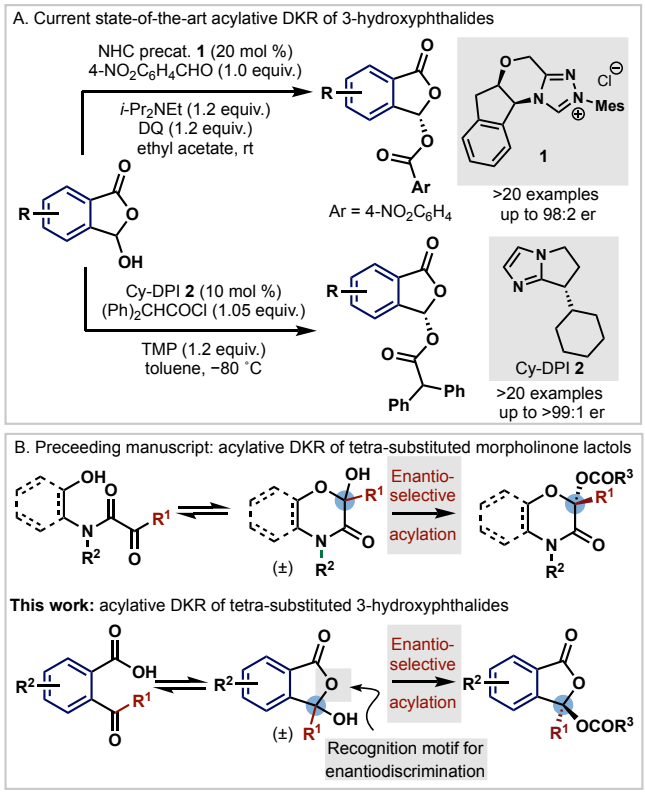
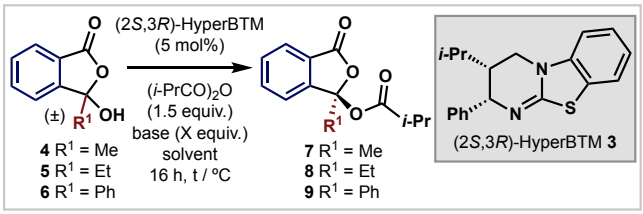



**Figure 2:** A. Previous state-of-the-art DKR approaches to generate enantioenriched tri-substituted 3-hydroxyphthalide esters. B. The preceeding manuscript and this work.

## 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$_2$NEt (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 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). Application of these conditions to a small range of 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 SI 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. The introduction of an aromatic C(3)-Ph substituent at the carbinol centre **6** resulted in only moderate yield but high enantioselectivity at room temperature (entry 13). Increasing the reaction temperature to 50 ˚C led to improved conversion while maintaining enantioselectivity, giving **9** in 82% yield and 94:6 er (entry 14).



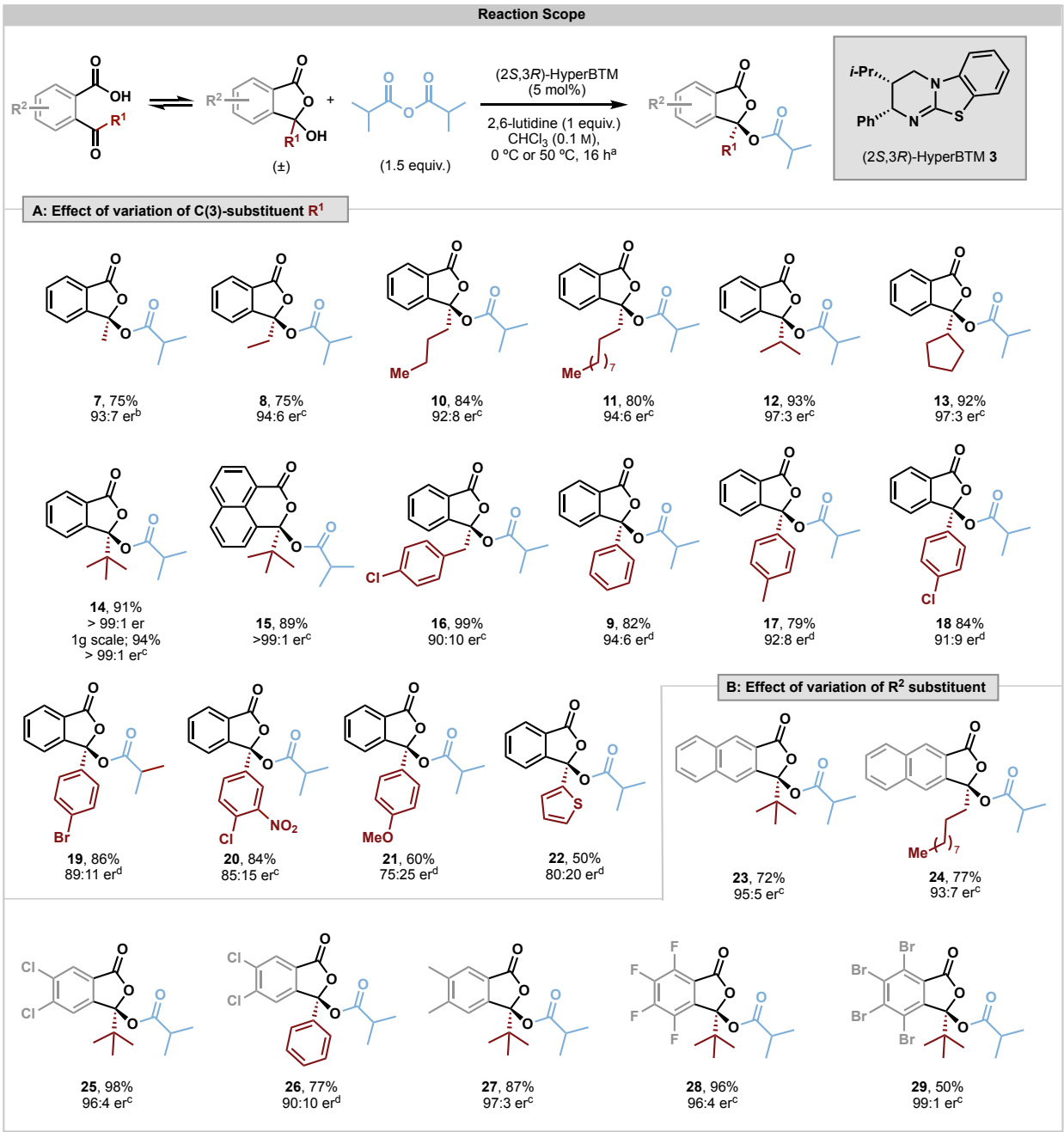

| Entry | $R^1$ | base (equiv.) | Solvent (0.1 M) | T / ˚C | Yield[a] | er[b] |
|---|---|---|---|---|---|---|
| 1 | Me (**4**) | *i*-Pr$_2$NEt (1.5) | toluene | rt | 57 | 65:35 |
| 2 | Me (**4**) | *i*-Pr$_2$NEt (1.5) | MeCN | rt | 66 | 62:38 |
| 3 | Me (**4**) | *i*-Pr$_2$NEt (1.5) | $CH_2Cl_2$ | rt | 81 | 80:20 |
| 4 | Me (**4**) | *i*-Pr$_2$NEt (1.5) | $CHCl_3$ | rt | 88 | 83:17 |
| 5 | Me (**4**) | *i*-Pr$_2$NEt (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 |

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.

**Scope and Limitations:**

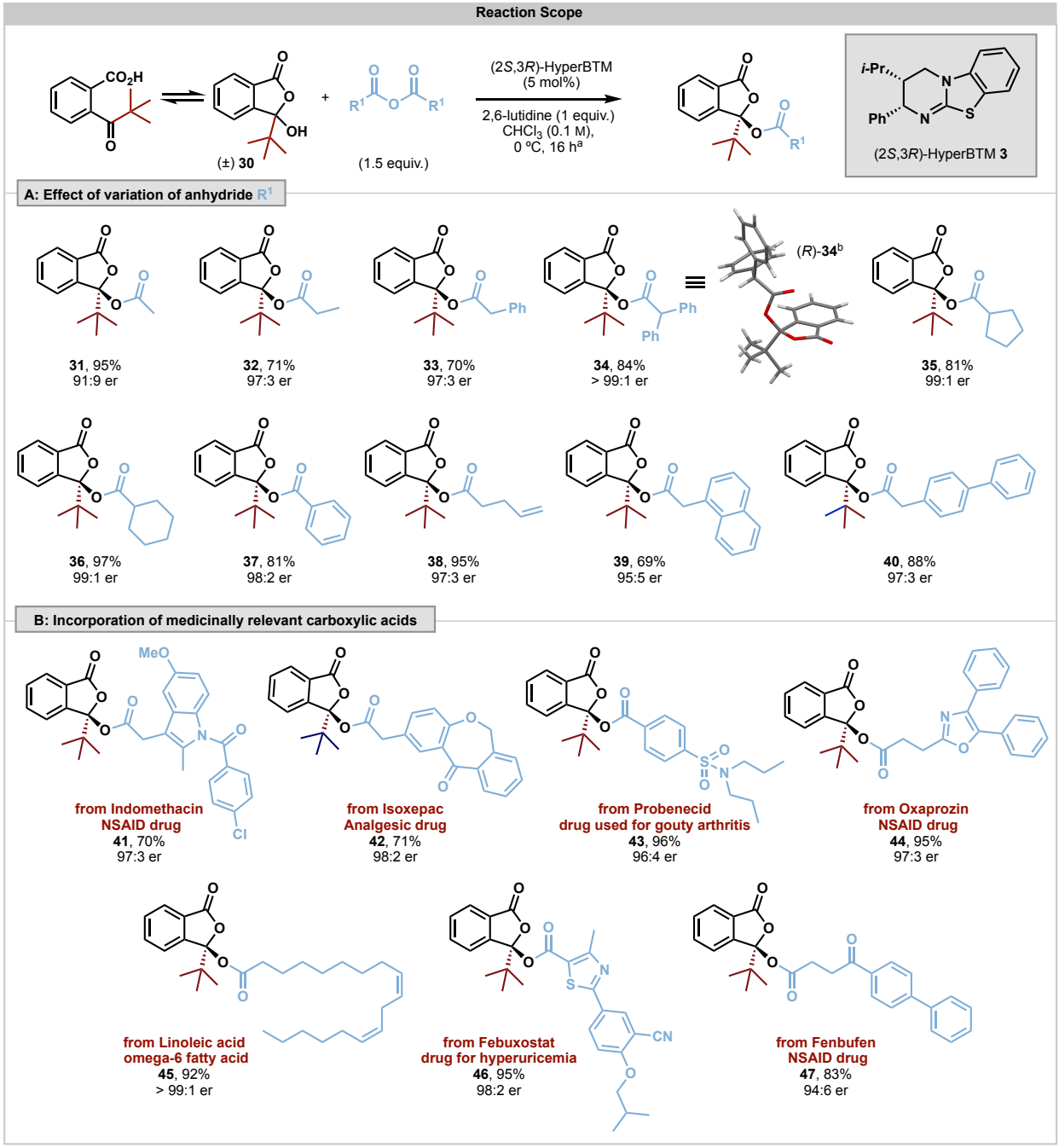
With proof-of-principle for this strategy demonstrated, the scope and limitations of the developed process was investigated (Scheme 1). Variation of the steric and electronic properties of the C(3)-substituent within the phthalide scaffold was initially varied (Scheme 1A). With aliphatic C(3)-substituents 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 (74% to 96% 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 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 at 50 ˚C, with C(3)-Ph, C(3)-4-Me$C_6H_4$, C(3)-4-Cl$C_6H_4$ and C(3)-4-Br$C_6H_4$, C(3)-4-Cl,3-$NO_2C_6H_3$ substitution giving the corresponding esters **9**, **17**-**20** in 82% to 86% yield and 85:15 to 94:6 er. C(3)-4-MeO$C_6H_4$ 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. 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.




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**.

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).




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.

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 and facilitating a DKR.

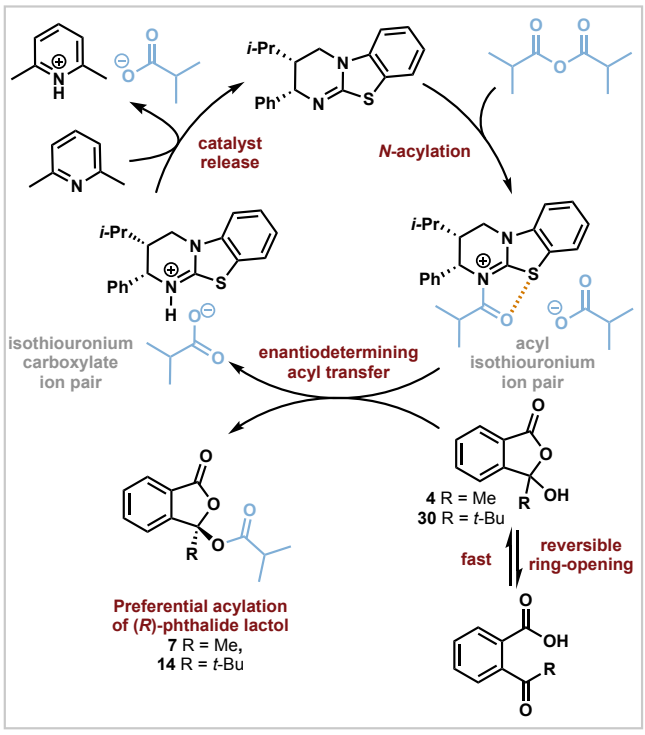



**Figure 3:** General mechanistic scheme for the observed acylative DKR.

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 SI for further information). The enantiomers of phthalide **30** could not be resolved satisfactorily by HPLC analysis and so its enantioselectivity could not be unambiguously determined. However, modelling using the DYNRES simulator developed by Faber and coworkers[17] 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[18] 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.[19] Building upon previous work,[20] an O•••S chalcogen bonding ($n_O$ to $\sigma^*_{S\text{-}C}$)[22-29] 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 acylated catalyst +NC-H substituent.[21] To deliver high enantioselectivity, a donor substrate motif is needed to promote enantiorecognition through interaction with the positively charged acylated isothiouronium intermediate.[18] 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.

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 3B). 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.

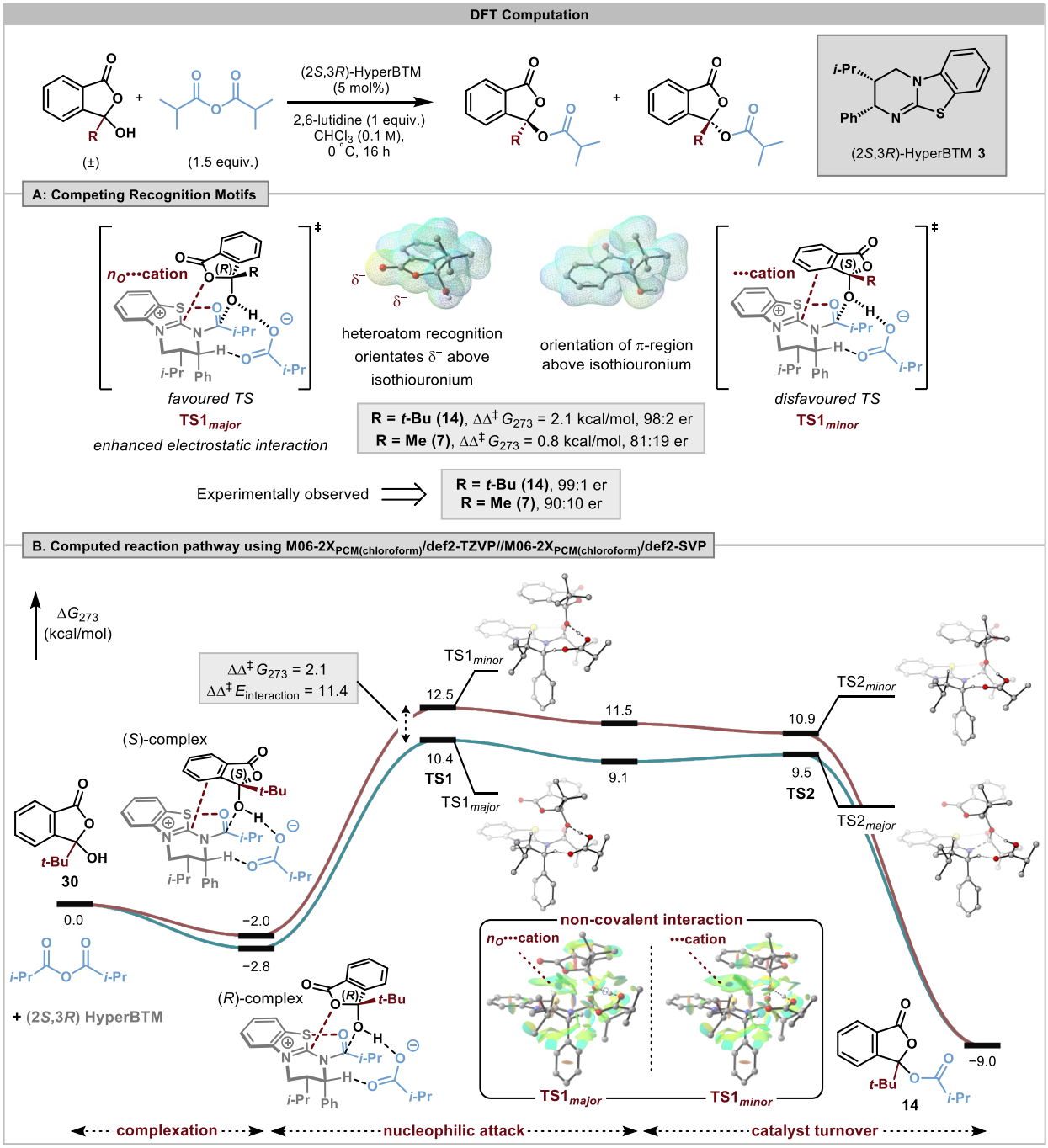



**Figure 4.** Computational studies of the DKR process. A. Competition of recognition motifs. Electrostatic potential maps generated with an isosurface of 0.2 and a colour scale from −0.2 a.u. (red) to +0.2 a.u. (blue). B. Reaction profile for the DKR to form **14** following reference.[20] $\Delta G_{273}$ at the level of M06-2X$_{PCM(chloroform)}$/def2-TZVP//M06-2X$_{PCM(chloroform)}$/def2-SVP in kcal/mol.

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 levels of 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. [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50]

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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 "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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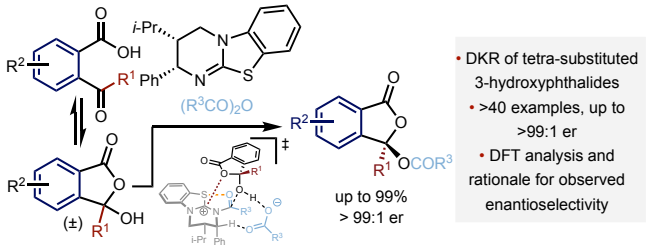
## Entry for the Table of Contents




The enantioselective isothiourea-catalysed acylative dynamic kinetic resolution of tetra-substituted 3-hydroxyphthalide derivatives using (2*S*,3*R*)-HyperBTM (5 mol%) as the catalyst (>40 examples in total) is reported. A diverse range of anhydrides, including those derived from bioactive and pharmaceutically relevant acids, can be tolerated in this process with the origin of enantioselectivity probed using DFT analysis.

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