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Enantioselective isothiurea-catalysed *trans*-dihydropyridinone synthesis using saccharin-derived ketimines: scope and limitations†

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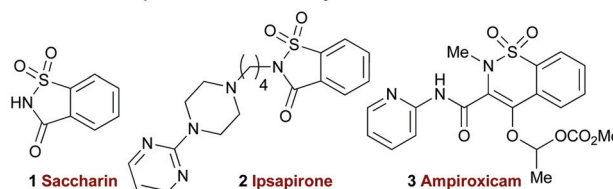
The catalytic enantioselective synthesis of a range of *trans*-dihydropyridinones from aryl-, heteroaryl- and alkenylacetic acids and saccharin-derived ketimines with good to excellent stereocontrol (15 examples, up to >95 : 5 dr, up to >99 : 1 er) is reported. After extensive optimisation, HyperBTM proved the optimal isothiurea catalyst for this transformation at −78 °C, giving *trans*-dihydropyridinones with generally excellent levels of diastereo- and enantioselectivity.

Introduction

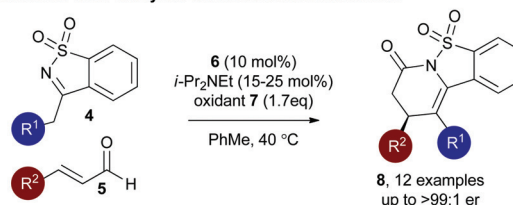
Saccharin (1,2-benzisothiazol-3-one-1,1-dioxide) **1** is a synthetic calorie-free additive, widely used as a sugar substitute in many food products and has proven an important discovery in the fight against diabetes.¹ The cyclic sulfonamide core motif embedded within saccharin has attracted much interest in recent decades from the medicinal chemistry community, with this motif a key constituent in many biologically active drugs (Fig. 1a). For example, saccharin-based sultams such as Ipsasipirone **2** are active agonists of 5-HT_{1A} receptors and have been applied as neuroprotectants and anxiolytics.² Current research within this area has led to the development of saccharin derivatives as inhibitors of carbonic anhydrase enzymes.³ Similarly, related cyclic sulfonamides such as Ampiroxicam **3** are bioactive.⁴

A number of enantioselective organocatalytic strategies have been explored to access chiral sultam products that incorporate the saccharin motif. For example, in 2012 Bode and co-workers developed an NHC-catalysed enantioselective annulation process utilising sulfonyl imine **4** and enals **5**, giving tricyclic sultams **7** in good to excellent yield (67–94%) and excellent enantioselectivity (90 : 10 to >99 : 1 er) using mono-substituted enals (Fig. 1b).⁵ Alternatively, Chen and co-workers have investigated an aza Diels–Alder reaction using organocatalytically-generated trienamines. Cyclic sulfonyl imine **10**

a. Saccharin and representative bioactive cyclic sulfonamides



b. Bode 2012: NHC-catalysed enantioselective annulation



c. Chen 2014: Amine-catalysed enantioselective annulation

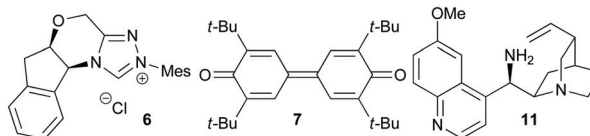
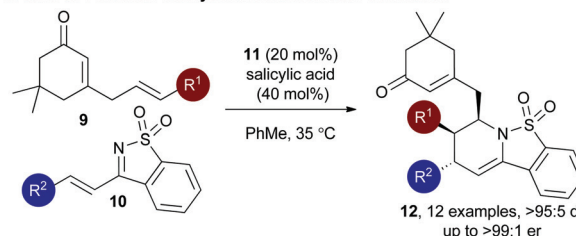


Fig. 1 Representative bioactive sultams and enantioselective organocatalytic strategies using saccharin derivatives to prepare cyclic sulfonamides.

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and cinchona alkaloid **11** (20 mol%) in the presence of salicylic acid generates a trienamine intermediate that can react through the δ,ϵ -alkene in an inverse electron demand Diels–Alder reaction with cyclic sulfonyl imines **9** to give products **12** in excellent diastereo- and enantioselectivity (>95 : 5 dr and 98 : 2 to >99 : 1 er, Fig. 1c).⁶

Following the pioneering nucleophile catalysed aldol lactonisation (NCAL) work of Romo and co-workers using carboxylic acids as ammonium enolate precursors,⁸ we developed the use of isothiureas⁹ for enantioselective Michael addition lactonisation processes directly from carboxylic acids.¹⁰ The generality of this concept has been extended to a range of formal intermolecular [4 + 2],¹¹ [3 + 2]¹² and [2 + 2]¹³ cycloaddition processes from carboxylic acids or anhydride starting materials (Fig. 2a).¹⁴ Of particular relevance to this manuscript we have previously accessed the dihydropyridinone motif from arylacetic acids through enantioselective Michael addition lactamisation using acyclic ketimines derived from chalcones¹⁵ and α,β -unsaturated γ -ketoesters.¹⁶ Based upon this work, in this manuscript the use of saccharin-derived cyclic ketimines as suitable substrates for the enantioselective preparation of polycyclic dihydropyridinones from aryl-, heteroaryl-, and alkenylacetic acids is investigated (Fig. 2b).

During the course of this work elegant studies from Pericás and co-workers reported a very similar reaction process. Using a polymer supported isothiurea catalyst (15 mol%), enantioselective annulation of a limited range of arylacetic acids as enolate precursors and saccharin-derived ketimines gave *trans*-dihydropyridinones in 86 : 14 to 96 : 4 dr and up to >99 : 1 er.¹⁷ Notably, no heteroaryl or alkenyl acetic acids were evaluated as ammonium enolate precursors within this process, and only limited substitution patterns within the arylacetic acid

component were included. Similarly, Ye and co-workers have recently reported a related NHC-catalysed process, utilising α -chloroaldehydes as azolium enolate precursors, giving *cis*-dihydropyridinones in >95 : 5 dr and >99 : 1 er upon reaction with saccharin-derived ketimines.¹⁸ This effective methodology is however limited to the use of alkyl- α -chloroaldehydes.

Results and discussion

Reaction optimisation

Optimisation studies began with evaluating a small range of isothiureas as catalysts for the synthesis of **15** using phenylacetic acid **13** and ketimine **14** as a model system. Using pivaloyl chloride to make an *in situ* mixed anhydride and (*R*)-BTM **16** (10 mol%) gave the desired product **15** in 71% yield, 85 : 15 dr and 92 : 8 er. Using (2*S*,3*R*)-HyperBTM **17** (10 mol%) at rt gave the desired product **15** in 64% yield, 84 : 16 dr and 90 : 10 er. The optimum catalyst, however, was (*S*)-tetramisole-HCl **18** (10 mol%) giving tricyclic sultam **15** in 73% yield, 85 : 15 dr and excellent 97.5 : 2.5 er. Attempts to lower the catalyst loading of (*S*)-tetramisole-HCl **18** to 5 mol% led to a reduced 56% isolated yield of **15** with 83 : 17 dr and 94 : 6 er. Alternative solvents such as EtOAc, THF and toluene were tested but gave poorer dr and er (entries 5–7), with poor solubility in toluene leading to a low product conversion (Table 1).

Further studies probed the generality of this enantioselective protocol using (*S*)-tetramisole-HCl **18** at rt through variation within the acid component, with arylacetic acids bearing both electron donating and withdrawing substituents,

Table 1 Enantioselective Michael addition–lactonisation optimisation

Entry	Catalyst (mol%)	Solvent	Yield ^a (%)	dr ^b	er ^c
1	16 (10)	CH ₂ Cl ₂	71	85 : 15	92 : 8 (<i>ent</i>)
2	17 (10)	CH ₂ Cl ₂	64	84 : 16	90 : 10 (<i>ent</i>)
3	18 (10)	CH ₂ Cl ₂	75	86 : 14	97.5 : 2.5
4	18 (5)	CH ₂ Cl ₂	65	85 : 15	97.5 : 2.5
5	18 (2)	CH ₂ Cl ₂	56	86 : 14	94 : 6
5	18 (10)	EtOAc	65	85 : 15	92 : 8
6	18 (10)	THF	61	85 : 15	92.5 : 7.5
7	18 (10)	PhMe	16	85 : 15	92 : 8

^a Isolated following column chromatography using Biotage® Isolera™ 4. ^b Determined by ¹H NMR spectroscopic analysis of crude reaction mixture. ^c Determined by chiral HPLC analysis.

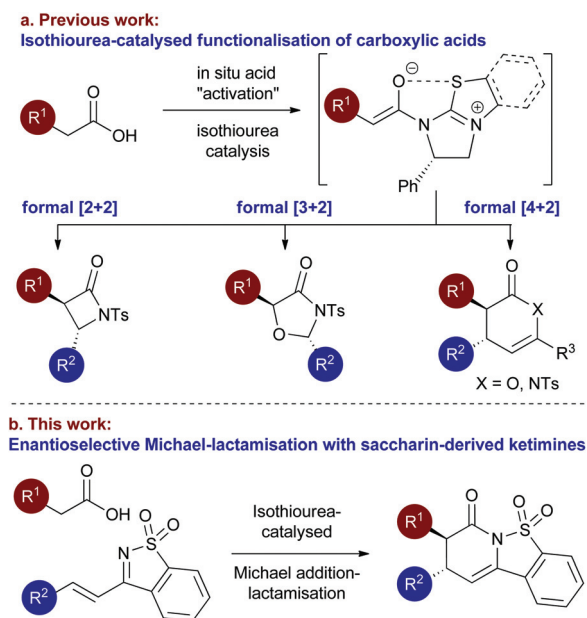


Fig. 2 Proposed Isothiurea-catalysed Michael addition–lactamisation using saccharin-derived ketimines.



as well as heteroarylacetic acids targeted. Although good conversion to product was observed in all cases, significant variation in product diastereo- and enantioselectivity was observed using (*S*)-tetramisole-HCl **18** at rt (conditions A, Table 2). For example, reaction with 4-bromophenyl acetic acid and *m*-tolyl acetic acid gave sultams **19** and **22** in 90 : 10 dr but moderate 80 : 20 and 75 : 25 er respectively. Use of 3-thiophenylacetic acid yielded the thienyl sultam product **23** in good 95 : 5 er but in moderate 74 : 26 dr. While 4-methoxyphenyl acetic acid gave **20** in acceptable dr and er, incorporating an electron withdrawing substituent in 4-trifluoromethylphenyl acetic acid led to reduced enantioselectivity (**21**, 90.5 : 9.5 er). These moderate and variable results indicated that the initial conditions identified in the catalyst screen using (*S*)-tetramisole-HCl **18** at rt were not general and that further optimisation was required.

Further optimisation probed the effect of lowering the reaction temperature to -78°C as this was predicted to minimise any competitive racemic background reaction over the range of substrates.¹⁹ Using (*S*)-tetramisole-HCl **18** (5 mol%) at -78°C (conditions B, Table 2) led to generally improved enantioselectivity. However, moderate er was observed for the formation of 3-MeC₆H₄-substituted derivative **22** (80 : 20 er), and poor diastereoselectivity for 3-thiophenyl substituted **23** (74 : 26 dr). Pleasingly, however, (2*R*,3*S*)-HyperBTM **17** (5 mol%) proved significantly more successful. 4-BrC₆H₄ substituted sultam **19** was produced in 81% yield, 93 : 7 dr and excellent

98.5 : 1.5 er. Sultams **20** and **21** incorporating the electron rich 4-MeOC₆H₄ and the electron withdrawing 4-CF₃C₆H₄ substituents were isolated in good yield, and excellent diastereo- and enantioselectivity. A dramatic improvement in enantioselectivity was observed for 3-MeC₆H₄-substituted derivative **22** (>99 : 1 er), while improved diastereoselectivity was observed for 3-thiophenyl derivative **23** (93 : 7 dr, >99 : 1 er).

Further substrate scope

With a reliable enantioselective process in hand using (2*R*,3*S*)-HyperBTM **17** at -78°C , the scope and limitations of this protocol was further investigated, with the extension to alternative heteroaryl and alkenylacetic acids targeted (Table 3). Variation of the carboxylic acid group showed that extended aromatic substituents are readily tolerated, with the 1-naphthyl unit incorporated to give **24** in 82% yield and 99 : 1 er. The incorporation of alkenyl substituents from the corresponding acids worked well, giving **25** and **26** in excellent dr. Consistent with our previous work the incorporation of the styrenyl unit within **25** led to reduced enantioselectivity (86 : 14 er) in comparison to **26** (>99 : 1 er).^{12b} The 3-indolyl unit was also readily included albeit with reduced diastereoselectivity (**27**, 80 : 20 dr) but excellent er (>99 : 1 er). Variation within the β -substituent of the saccharin-derived ketimine was next evaluated (products **28–32**). The 1-naphthyl unit was readily incorporated, as were electron-donating and -withdrawing 4-substituents, as well as

Table 2 Probing the Michael addition–lactamisation process^{a,b,c}

Conditions: 		
A: 18 (5 mol%) <i>i</i> -Pr ₂ NEt (1.0 eq), rt, 2 hours	B: 18 (5 mol%) <i>i</i> -Pr ₂ NEt (1.0 eq), -78°C , 4 hours	C: 17 (5 mol%) <i>i</i> -Pr ₂ NEt (1.0 eq), -78°C , 4 hours
 15 A: 65%, 85:15 dr, 97.5:2.5 er B: 65%, 85:15 dr, 97.5:2.5 er C: 68% 85:15 dr, 97.5:2.5 er	 19 A: 72%, 90:10 dr, 80:20 er B: 80%, 90:10 dr, 90.5:9.5 er C: 81%, 93:7 dr, 98.5:1.5 er	 20 A: 65%, 90:10 dr, 94.5:5.5 er B: 74%, 90:10 dr, 99:1 er C: 75%, >95:5 dr, >99:1 er
 21 A: 59%, 94:6 dr, 90.5:9.5 er B: 64%, 94:6 dr, 93:7 er C: 64%, 94:6 dr, 98.5:1.5 er	 22 A: 64%, 90:10 dr, 75:25 er B: 70%, 90:10 dr, 80:20 er C: 71%, 94:6 dr, >99:1 er	 23 A: 64%, 74:26 dr, 95:5 er B: 78%, 74:26 dr, >99:1 er C: 77%, 93:7 dr, >99:1 er

^a Isolated yield. ^b dr determined by ¹H NMR of the crude reaction product. ^c er determined by chiral HPLC.

Table 3 Probing the generality of the Michael addition–lactamisation process^{a,b,c}

 24 , 82% 90:10 dr, 99:1 er	 25 , 64% >95:5 dr, 86:14 er	 26 , 77% 96:4 dr, >99:1 er
 27 , 60%, 80:20 dr, >99:1 er	 28 , 99% 90:10 dr, >99:1 er	 29 , 84% 88:12 dr, 97.5:2.5 er
 30 , 51% 94:6 dr, >99:1 er	 31 , 69% 94:6 dr, >99:1 er	 32 , 92% 93:7 dr, 95:5 er

^a Isolated yield. ^b dr determined by ¹H NMR of the crude reaction product. ^c er determined by chiral HPLC.



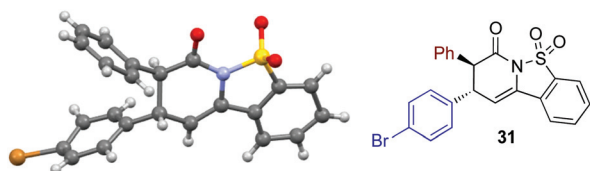
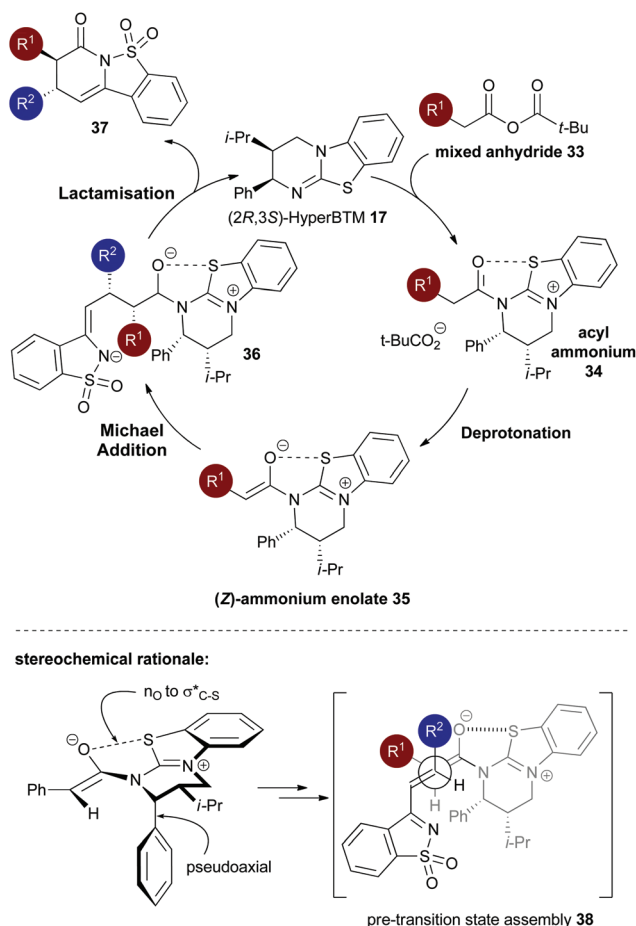


Fig. 3 Molecular representation of the X-ray structure of **31**.



Scheme 1 Proposed mechanism and stereochemical rationale of the isothiurea-catalysed Michael addition–lactamisation.

the 2-furyl motif with good to excellent diastereo- and enantioselectivity.²⁰

The relative and absolute configuration within **31** was assigned by X-ray crystallography analysis, with the configuration within all other products assigned by analogy (Fig. 3).²¹

Proposed mechanism

Consistent with our previous studies, a proposed catalytic cycle for the synthesis of these saccharin-derived dihydropyridones is shown in Scheme 1. Initial *in situ* formation of the mixed anhydride **33** from pivaloyl chloride and the carboxylic acid, followed by subsequent nucleophilic attack from the (2*R*,2*S*)-HyperBTM catalyst **17** generates acyl ammonium ion

34. Deprotonation to form the corresponding (*Z*)-ammonium enolate **35**, followed by stereoselective Michael addition gives **36**, with lactonisation releasing catalyst **17** and the polycyclic dihydropyranone product **37**. A stabilising n_{O} to $\sigma_{\text{C-S}}^*$ interaction between the enolate oxygen and the sulfur of the isothiuronium ion is proposed to lock the conformation of the enolate species,²² forcing the adjacent stereodirecting phenyl substituent to adopt a pseudoaxial orientation to minimise 1,2-strain.²³ Subsequent Michael addition occurs preferentially *anti*- to this stereodirecting group, with the two prostereogenic centres adopting an approximately staggered array to minimise unfavourable non-bonding interactions. By analogy to Heathcock's model²⁴ a pre-transition state assembly **38** is consistent with the observed sense of diastereo- and enantioselectivity.

Conclusions

In conclusion, the catalytic enantioselective synthesis of a range of saccharin-derived *trans*-dihydropyridinones (15 examples, up to >95 : 5 dr, up to >99 : 1 er) using both aryl-, heteroaryl-, and alkenylacetic acids as ammonium enolate precursors using (2*R*,3*S*)-HyperBTM has been developed. Further work from this laboratory is directed toward developing alternative uses of isothiureas and other Lewis bases in enantioselective catalysis.

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Notes and references

- (a) K. Köhler, A. Hillebrecht, J. Schulze Wischeler, A. Innocenti, A. Heine, C. T. Supuran and G. Klebe, *Angew. Chem., Int. Ed.*, 2007, **46**, 7697–7699; (b) J. Moeker, T. S. Peat, L. F. Bornaghi, D. Vullo, C. T. Supuran and S.-A. Poulsen, *J. Med. Chem.*, 2014, **57**, 3522–3531.
- R. J. Fanelli, T. Schuurman, T. Glaser and J. Traber, *Prog. Clin. Biol. Res.*, 1990, **361**, 461–467.
- (a) M. D'Ascenzio, S. Carradori, C. De Monte, D. Secci, M. Ceruso and C. T. Supuran, *Bioorg. Med. Chem.*, 2014, **22**, 1821–1831; (b) S. Carradori, D. Secci, C. De Monte, A. Mollica, M. Ceruso, A. Akdemir, A. P. Sobolev, R. Codispoti, F. De Cosmi, P. Guglielmi and C. T. Supuran, *Bioorg. Med. Chem.*, 2016, **24**, 1095–1105.
- L. Levy, *Drugs Future*, 1992, **17**, 451–454.
- A. G. Kravina, J. Mahatthananchai and J. W. Bode, *Angew. Chem., Int. Ed.*, 2012, **51**, 9433–9436.



- 6 X. Feng, Z. Zhou, C. Ma, X. Yin, R. Li, L. Dong and Y.-C. Chen, *Angew. Chem., Int. Ed.*, 2013, **52**, 14173–14176.
- 7 The research data underpinning this publication can be accessed at DOI: 10.17630/12aeb23b-e4ae-402c-a9da-f7fc0b17d374.
- 8 (a) G. S. Cortez, R. L. Tennyson and D. Romo, *J. Am. Chem. Soc.*, 2001, **123**, 7945–7946; (b) S. H. Oh, G. S. Cortez and D. Romo, *J. Org. Chem.*, 2005, **70**, 2835–2838.
- 9 For seminal work on isothioureia catalysis in kinetic resolution and acyl transfer reaction processes see: (a) V. B. Birman and X. Li, *Org. Lett.*, 2006, **8**, 1351–1354; (b) V. B. Birman, H. Jiang, X. Li, L. Guo and E. W. Uffman, *J. Am. Chem. Soc.*, 2006, **128**, 6536–6537; (c) M. Kobayashi and S. Okamoto, *Tetrahedron Lett.*, 2006, **47**, 4347–4350; (d) V. B. Birman and X. Li, *Org. Lett.*, 2008, **10**, 1115–1118; (e) Y. Zhang and V. B. Birman, *Adv. Synth. Catal.*, 2009, **351**, 2525–2529; (f) C. Joannes, C. P. Johnston, C. Concellón, C. Simal, D. Philp and A. D. Smith, *Angew. Chem., Int. Ed.*, 2009, **48**, 8914–8918. For recent reviews, see: (g) L. C. Morrill and A. D. Smith, *Chem. Soc. Rev.*, 2014, **43**, 6214–6226; (h) J. E. Taylor, S. D. Bull and J. M. J. Williams, *Chem. Soc. Rev.*, 2012, **41**, 2109–2121. For a selection of alternative isothioureia-catalysed processes see below. For reactions utilising α,β -unsaturated acyl ammonium intermediates see: (i) E. R. T. Robinson, C. Fallan, C. Simal, A. M. Z. Slawin and A. D. Smith, *Chem. Sci.*, 2013, **4**, 2193–2200; (j) S. Vellalath, K. N. Van and D. Romo, *Angew. Chem., Int. Ed.*, 2013, **52**, 13688–13693; (k) G. Liu, M. E. Shirley, K. N. Van, R. L. McFarlin and D. Romo, *Nat. Chem.*, 2013, **5**, 1049–1057; (l) Y. Fukata, K. Asano and S. Matsubara, *J. Am. Chem. Soc.*, 2015, **137**, 5320–5323. For ammonium ylide intermediates see: (m) T. H. West, D. S. B. Daniels, A. M. Z. Slawin and A. D. Smith, *J. Am. Chem. Soc.*, 2014, **136**, 4476–4479.
- 10 For select examples see: (a) D. G. Stark, T. J. C. O’Riordan and A. D. Smith, *Org. Lett.*, 2014, **16**, 6496–6499; (b) S. R. Smith, S. M. Leckie, R. Holmes, J. Douglas, C. Fallan, P. Shapland, D. Pryde, A. M. Z. Slawin and A. D. Smith, *Org. Lett.*, 2014, **16**, 2506–2509; (c) P.-P. Yeh, D. S. B. Daniels, D. B. Cordes, A. M. Z. Slawin and A. D. Smith, *Org. Lett.*, 2014, **16**, 964–967; (d) D. G. Stark, L. C. Morrill, P.-P. Yeh, A. M. Z. Slawin, T. J. C. O’Riordan and A. D. Smith, *Angew. Chem., Int. Ed.*, 2013, **52**, 11642–11646; (e) L. C. Morrill, J. Douglas, T. Lebl, A. M. Z. Slawin, D. J. Fox and A. D. Smith, *Chem. Sci.*, 2013, **4**, 4146–4155; (f) L. C. Morrill, T. Lebl, A. M. Z. Slawin and A. D. Smith, *Chem. Sci.*, 2012, **3**, 2088–2093; (g) D. Belmessieri, L. C. Morrill, C. Simal, A. M. Z. Slawin and A. D. Smith, *J. Am. Chem. Soc.*, 2011, **133**, 2714–2720.
- 11 (a) L. Hespings, A. Biswas, C. G. Daniliuc, C. Muck-Lichtenfeld and A. Studer, *Chem. Sci.*, 2015, **6**, 1252–1257; (b) S. R. Smith, C. Fallan, J. E. Taylor, R. McLennan, D. S. B. Daniels, L. C. Morrill, A. M. Z. Slawin and A. D. Smith, *Chem. – Eur. J.*, 2015, **21**, 10530–10536.
- 12 (a) S. R. Smith, J. Douglas, H. Prevet, P. Shapland, A. M. Z. Slawin and A. D. Smith, *J. Org. Chem.*, 2014, **79**, 1626–1639; (b) L. C. Morrill, S. M. Smith, A. M. Z. Slawin and A. D. Smith, *J. Org. Chem.*, 2014, **79**, 1640–1655.
- 13 J.-Y. Bae, H.-J. Lee, S.-H. Youn, S.-H. Kwon and C.-W. Cho, *Org. Lett.*, 2010, **12**, 4352.
- 14 L. C. Morrill, L. A. Ledingham, J.-P. Couturier, J. Bickel, A. D. Harper, C. Fallan and A. D. Smith, *Org. Biomol. Chem.*, 2014, **12**, 624–636.
- 15 C. Simal, T. Lebl, A. M. Z. Slawin and A. D. Smith, *Angew. Chem., Int. Ed.*, 2012, **51**, 3653–3657.
- 16 P.-P. Yeh, D. S. B. Daniels, C. Fallan, E. Gould, C. Simal, J. E. Taylor, A. M. Z. Slawin and A. D. Smith, *Org. Biomol. Chem.*, 2015, **13**, 2177–2191.
- 17 J. Izquierdo and M. A. Pericàs, *ACS Catal.*, 2016, **6**, 348–356.
- 18 Z.-Q. Liang, D.-L. Wang, C.-L. Zhang and S. Ye, *Org. Biomol. Chem.*, 2016, DOI: 10.1039/c6ob01040g.
- 19 Treatment of 4-bromophenyl acetic acid with pivaloyl chloride, *i*-Pr₂NEt and ketimine **14**, gave 24% conversion into corresponding product **19** (as determined by ¹H NMR spectroscopic analysis). This confirms the presence of a base-catalysed racemic background reaction at room temperature.
- 20 No reaction was observed in this process using alkyl substituted carboxylic acids. We were unable to prepare alkyl substituted ketimines for their use in this transformation.
- 21 The crystallographic data obtained for **31** has been deposited with the Cambridge Crystallographic Data Centre and the supplementary data can be found via CCDC 1491707.
- 22 For the initial postulate of 1,5-S...O interactions as a control element in isothioureia catalysis see: (a) V. B. Birman, X. Li and Z. Han, *Org. Lett.*, 2007, **9**, 37–40. For other manuscripts of interest see: (b) M. E. Abbasov, B. M. Hudson, D. J. Tantillo and D. Romo, *J. Am. Chem. Soc.*, 2014, **136**, 4492–4495; (c) P. Liu, X. Yang, V. B. Birman and K. N. Houk, *Org. Lett.*, 2012, **14**, 3288–3291. Romo and Tantillo (ref. 22b) have probed the nature of 1,5-S...O interactions of α,β -unsaturated acyl ammonium species with NBO and postulate this interaction is due to a number of orbital interactions. In particular, unfavourable $n_s \leftrightarrow \sigma_{C-H}^*/\sigma_{C-H}$ interactions disfavour alternative conformations with an O–C–N–C dihedral angle of 180°.
- 23 For representative examples that demonstrate the preference of substituents adjacent to an *N*-acyl group in heterocyclic compounds to adopt a pseudo-axial position see: (a) P. J. Sinclair, D. Zhai, J. Reibenspies and R. M. J. Williams, *J. Am. Chem. Soc.*, 1986, **108**, 1103; (b) J. F. Dellaria and B. D. Santarsiero, *J. Org. Chem.*, 1989, **54**, 3916; (c) M. G. B. Drew, L. M. Harwood, G. Park, D. W. Price, S. N. G. Tyler, C. R. Park and S. G. Cho, *Tetrahedron*, 2001, **57**, 5641.
- 24 For an excellent overview of this area see: (a) D. A. Oare and C. H. Heathcock, *Top. Stereochem.*, 1989, **19**, 227–407. For



select representative examples of enolate additions to Michael acceptors see: (b) C. H. Heathcock, M. A. Henderson, D. A. Oare and M. A. Sanner, *J. Org. Chem.*, 1985, **50**, 3019–3022; (c) D. A. Oare, M. A. Henderson, M. A. Sanner and C. H. Heathcock,

J. Org. Chem., 1990, **55**, 132–157; (d) M. Yamaguchi, M. Tsukamoto, S. Tanaka and I. Hirao, *Tetrahedron Lett.*, 1984, **25**, 5661–5664. For a computational investigation of intermolecular Michael reactions see: (e) E. E. Kwan and D. A. Evans, *Org. Lett.*, 2010, **12**, 5124–5127.

