Organic & Biomolecular Chemistry

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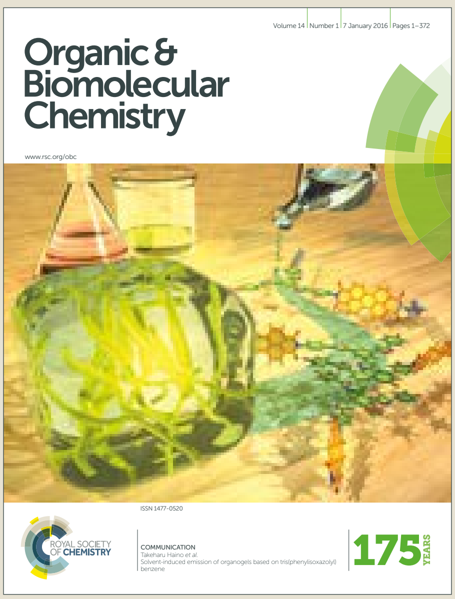

Journal Name ARTICLE

View Article Online
DOI: 10.1039/C9OB00703B

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Evaluating Aryl Esters as Bench-Stable C(1)-Ammonium Enolate Precursors in Catalytic, Enantioselective Michael Addition-Lactonisations

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An evaluation of a range of aryl, alkyl and vinyl esters as prospective C(1)-ammonium enolate precursors in enantioselective Michael addition-lactonisation processes with (*E*)-trifluoromethylenones using isothiourea catalysis is reported. Electron deficient aryl esters are required for reactivity, with 2,4,6-trichlorophenyl esters providing optimal product yields. Catalyst screening showed that tetramisole was the most effective isothiourea catalyst, giving the desired dihydropyranone product in excellent yield and stereoselectivity (up to 90:10 dr and 98:2 er). The scope and limitations of this process have been evaluated, with a range of diester products being generated after ring-opening with MeOH to give stereodefined dihydropyranones with excellent stereocontrol (10 examples, typically ~90:10 dr and >95:5 er).

Introduction

C(1)-Ammonium enolates are valuable reactive intermediates in a variety of diastereo- and enantioselective reactions catalysed by chiral tertiary amine Lewis bases.[1] In early reports, C(1)-ammonium enolates were generated by the interception of an isolated di-substituted ketene or in situ-generated mono-substituted ketene by a tertiary amine catalyst (Fig. 1).[2] More recently, techniques have been developed to generate C(1)-ammonium enolates in situ that avoid the use of highly reactive ketenes. These processes rely upon derivatisation of bench-stable carboxylic acids to generate reactive acylating agents (such as mixed anhydrides) that readily react with tertiary amine catalysts. Subsequent deprotonation of the resulting *N*-acyl ammonium species generates the desired C(1)-ammonium enolate (Fig. 1). Alongside other tertiary amine catalysts, chiral isothioureas have been used extensively as efficient Lewis base catalysts in a range of processes that proceed via an ammonium enolate intermediate.[3,4] For example, a model enantioselective Michael addition-lactonisation process using trifluoromethylenone **1** to form stereodefined dihydropyranones **2**(Fig. 2a) has been investigated using a range of C(1)-ammonium enolate precursors (Fig. 2b).[5,6,7] Carboxylic acids can be derivatised in situ through treatment with pivaloyl chloride (1.5 equiv.) and *i*-Pr_2NEt (4 equiv.) to generate a mixed anhydride as an enolate precursor.[5] This protocol generates dihydropyranone **2** in good yield and excellent stereoselectivity, however the pivalic anhydride by-product is difficult to separate from the desired product. This approach also relies on using an excess of reagents to facilitate an efficient in situ activation protocol. Bench-stable symmetric carboxylic anhydrides can also be employed as C(1)-ammonium enolate precursors.[6] This avoids the requirement for large excesses of additional reagents and minimises side-product formation, although the protocol formally requires two equivalents of the carboxylic acid precursor, which could be a limitation when using complex or expensive acid components. Acyl imidazoles can also be used in isothiourea-catalysed Michael addition-lactonisation reactions, under base-free conditions.[7] However, this process typically requires high catalyst loadings (20 mol%) and long reaction times to form the dihydropyranone products in slightly reduced yields compared with acid precursors. Notably, the optimal isothiourea catalyst varies with the enolate precursor, with HyperBTM **3** favoured with both carboxylic acids and symmetric anhydrides, while BTM·HCl **4·HCl** is optimal when using acyl imidazoles.

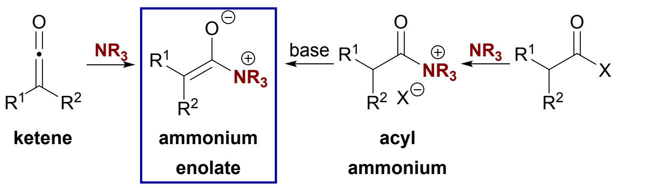

Figure 1: Strategies for ammonium enolate formation

Previous mechanistic and computational studies suggest that the nature of the leaving group of the ammonium enolate precursor is not only important for the initial catalyst acylation, but that it is also required for deprotonation of the resulting *N*-acyl ammonium.[5,8] When considering alternative ammonium enolate processes at the carboxylic acid oxidation level it is likely that the leaving group would also need to fulfil this dual requirement. Electron deficient aryl esters are effective acylating agents[9] and have been previously investigated as C(1)-ammonium and -azolium enolate precursors.[10] Within the field of isothiourea catalysis, aryl esters have been used for the formation of α,β-acyl ammonium intermediates[11] and have found particular utility in processes where the aryloxide leaving

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† Electronic supplementary information (ESI) available: Experimental procedures, product characterisation data (mpt, NMR, IR, HRMS, $[a]_D$, HPLC) and traces (NMR, HPLC) can be found at DOI: https://doi.org/10.17630/cb133261-b58e-4d72-b380-c877c993dc5d[23]

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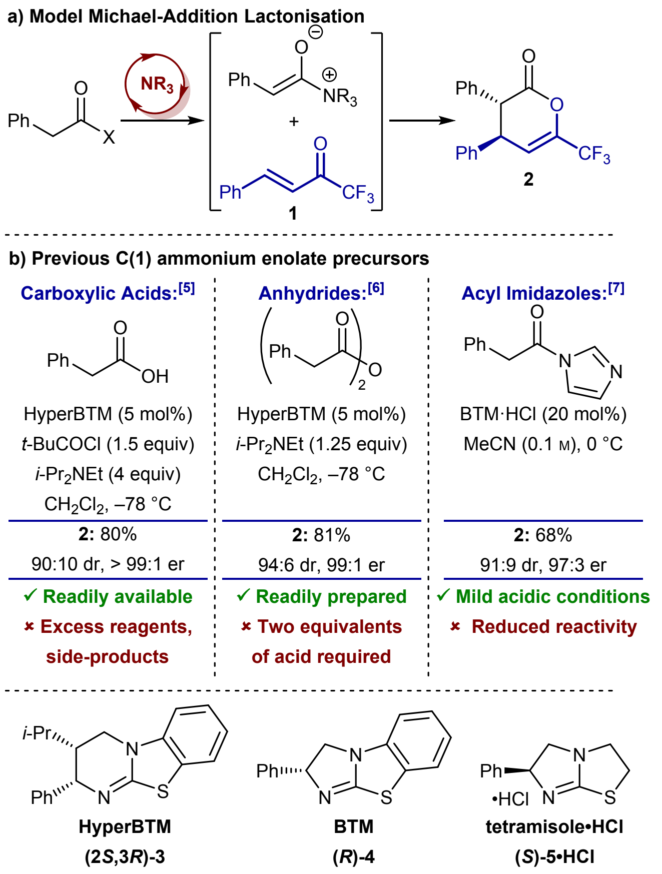

Figure 2: Ammonium enolate precursors in isothiourea-catalysed Michael addition-lactonisation reactions.

group is subsequently required to act as a nucleophile to facilitate catalyst turnover.[12] For example, 4-nitrophenyl esters have been used as substrates in stereoselective [2,3]-sigmatropic rearrangements,[13,8b] as well as enantioselective additions to iminium ions[14] and in α,β-unsaturated acyl ammonium catalysis.[15] Stable pentafluorophenyl esters have also been used as ammonium enolate precursors in dual catalytic α-functionalisation processes developed by the groups of Snaddon,[16] Hartwig[17] and Gong.[18]

To date, the use of ester substrates in isothiourea-catalysed formal [4+2] cycloaddition processes proceeding via an ammonium enolate have yet to be explored. In this manuscript, we report the investigation of various bench-stable esters as C(1)-ammonium enolate precursors for Michael addition-lactonisation reactions using trifluoromethylenones as model electrophiles (Fig. 3).

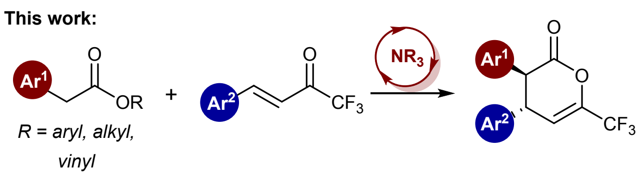

Figure 3: Esters as precursors in isothiourea-catalysed Michael addition-lactonisation reactions.

Results and discussion

(i) Screening and Optimisation

Initially, the isothiourea-catalysed reaction between trifluoromethylenone **1** and various potential ammonium enolate precursors to form dihydropyranone **2** was studied. To investigate the feasibility of alkyl esters as precursors, trifluoroethyl ester **6** was subjected to representative conditions [**(*S*)-5·HCl** (20 mol%) and *i*-Pr_2NEt (2.5 equiv.) in CH_2Cl_2 at rt for 16 h]; while vinyl ester **7** was also evaluated due to its known ability to act as an acyl transfer agent.[9] Both esters gave < 5% conversion to product and were not evaluated further (Table 1, Entries 1 and 2). To investigate if an electron-deficient aryl ester was required, a number of electron-deficient aryl (4-$NO_2C_6H_4$, C_6F_5, 3,5-$(CF_3)_2C_6H_3$, 3,4,5-$F_3C_6H_2$, 2,4,6-$Cl_3C_6H_2$) phenylacetic ester derivatives **8**–**12** were prepared from phenylacetyl chloride and the requisite phenol, alongside phenyl ester **13.** The aryl esters were then screened in our model reaction (Table 1, Entries 3–8). Electron deficient aryl esters (**8**-**12**) gave the desired dihydropyranone in significant yield (> 10%) (determined by NMR analysis of the crude material using 1,4-dinitrobenzene as an internal standard) while phenyl ester **13** gave no conversion.[19] Where significant yield was observed, dihydropyranone **2** was generally formed in good dr (> 84:16) and er (> 81:19) (Table 1, Entries 3–7). In particular, trichlorophenyl ester **12** provided dihydropyranone **2** in good 63% yield along with a promising 84:16 dr and 87:13 er for the major diastereoisomer (Table 1, Entry 7). This suggests that the aryloxide generated following acylation of catalyst by ester **12** is both a sufficient leaving group for acyl ammonium formation and a suitable base to promote ammonium enolate formation. Notably, trichlorophenyl esters have also previously been found to be optimal for methods in α,β-unsaturated acyl ammonium catalysis, where the aryloxide is not required to operate as a nucleophile.[11,20]

Further optimisation of the reaction with trichlorophenyl ester **12** was then investigated (Table 2).[21] First, the reaction concentration was increased to 0.2 M resulting in a yield of 57% of **2** in 5 h at RT with no significant reduction in diastereo- or enantioselectivity (87:13 dr, 88:12 er) (Table 2, Entry 1). In the absence of catalyst, only starting materials were recovered (Table 2, Entry 2). Changing the solvent to THF improved the product er (97:3) while maintaining a good yield (55%) (Table 2, Entry 3). The use of BTM **4** as catalyst gave comparable results to tetramisole·HCl **5·HCl** (Table 2, Entry 4), while HyperBTM **3** gave a drop in both yield and enantioselectivity (Table 2, Entry 5). Changing the stoichiometry of auxiliary base and ester to 1 and 2 equivalents respectively and performing the reaction at 0 °C over 16 h, gave dihydropyranone **2** with excellent stereoselectivity (89:11 dr, 98:2 er) and in good yield (79%) as a

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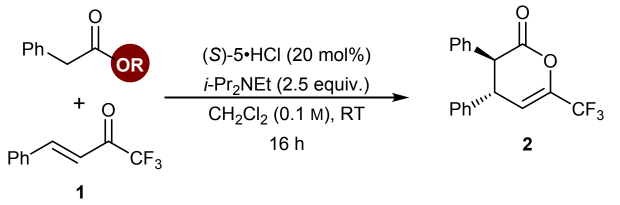
Table 1: Results of acylating agent screen.



Entry	R	Yield (%)[a]	dr[b]	er[c]
1	CF_3CH_2 **6**	<5%	n/d	n/d
2	CH_2=CH **7**	<5%	n/d	n/d
3	4-$NO_2C_6H_4$ **8**	32	87:13	83:17
4	C_6F_5 **9**	26	87:13	85:15
5	3,5-$(CF_3)_2C_6H_3$ **10**	16	88:12	81:19
6	3,4,5-$F_3C_6H_2$ **11**	11	87:13	81:19
7	2,4,6-$Cl_3C_6H_2$ **12**	63	84:16	87:13
8	C_6H_5 **13**	<5%	n/d	n/d

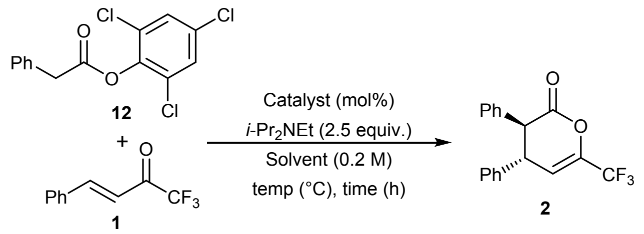
[a] Yield determined by ^{1}H NMR spectroscopic analysis using 1,4-dinitrobenzene as internal standard. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] (3*S*,4*S*):(3*R*,4*R*). Determined by chiral HPLC analysis.

mixture of diastereoisomers (Table 2, Entry 6). Under these conditions, the catalyst loading could be reduced to 10 mol% without compromising the yield (96%) or stereoselectivity (dr 89:11, er 98:2) (Table 2, Entry 7). This yield and high stereoselectivity compares favourably with those previously reported for other C(1)-ammonium enolate precursors, however, a long reaction time (48 h) was required. Attempts to lower the catalyst loading to 5 mol% compromised the yield in this case (Table 2, Entry 8).

(ii) Scope and Limitations

Under the optimised conditions, the scope and limitations of the process were explored using various trichlorophenyl arylacetic esters and substituted trifluoromethylenones (Table 3). The crude dr of the reaction products was generally high (around 90:10), while the products were isolated as an inseparable mixture of diastereoisomers. The er of the major diastereoisomer is reported in each case. Incorporation of a strongly electron-withdrawing 4-trifluoromethyl substituent on the arylacetic ester was well tolerated, giving dihydropyranone **14** in good yield (75%) and 90:10 er (Table 3a). An arylacetic ester bearing an electron-donating 4-methoxy substituent gave 50% yield of dihydropyranone **15** in an excellent 95:5 er. The scope was further explored, and the utility of the protocol extended by carrying out in situ methanolysis of the dihydropyranone products by addition of excess methanol after the catalysis. The ring-opened methyl ester products were more stable to column chromatography than the corresponding dihydropyranones, leading to more consistent and representative results (Table 3b). Keto-ester **16** was isolated as

Table 2: Reaction optimisation.



Entry	Solvent	Temp.	Time (h)	Catalyst (%)	Yield (%)[a]	dr[b]	er[c]
1	CH_2Cl_2	RT	5	**5·HCl** (20)	53	87:13	88:12
2	CH_2Cl_2	RT	5	—	0	n/d	n/d
3	THF	RT	5	**5·HCl** (20)	55	84:16	97:3
4	THF	RT	5	**4** (20)	53	86:14	4:96
5	THF	RT	5	**3** (20)	41	88:12	10:90
6[d]	THF	0 °C	16	**5·HCl** (20)	79[e]	89:11	98:2
7[d]	THF	0 °C	48	**5·HCl** (10)	96[e]	89:11	98:2
8[d]	THF	0 °C	48	**5·HCl** (5)	76[e]	91:9	95:5

[a] Unless stated, determined by ^{1}H NMR spectroscopic analysis using 1,4-dinitrobenzene as internal standard. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] (3*S*,4*S*):(3*R*,4*R*). Determined by chiral HPLC analysis. [d] *i*-Pr_2NEt (1.0 equiv.), **12** (2.0 equiv.), [e] Isolated yield.

a mixture of diastereoisomers in excellent 86% yield and 97:3 er after the two-step protocol. Electron-withdrawing arylacetic substituents on the ester were again well tolerated, with keto-esters **17** (4-trifluoromethyl) and **18** (4-bromo) isolated in good yields (77% and 73% respectively) and enantioselectivity (93:7 and 97:3 er respectively). Electron-donating substituents gave mixed results with 4-methoxy substituted keto-ester **19** isolated in 73% yield and 97:3 er, while incorporation of a more electron-donating 4-dimethylamino group only gave moderate 51% yield of **20** after prolonged reaction time (6 days, some **1** remaining) however high er (99:1) was observed. A 2-naphthyl substituent was also tolerated, giving keto-ester **21** in good 72% yield and 97:3 er. Variation of the substitution on the aryl group of the enone was then explored (Table 3c). Again, the introduction of electron withdrawing substituents was well tolerated with 4-bromo **22** and 3-methoxy **23** substitution giving the corresponding products in good yields (69% and 86% respectively) and with high enantioselectivity (95:5 and 94:6 for **22** and **23** respectively). Substitution of the aryl ring with an electron-donating group led to good yield of 4-Me **24** (62%) with high enantioselectivity (96:4 er). Finally, a heterocycle-substituted product **25** was also isolated in good yield (69%) and excellent 98:2 er albeit it in a lower 71:29 crude dr.

Based upon our previous reports, a mechanism for this process can be postulated. The reaction proceeds through initial acylation of catalyst **5** by trichlorophenyl ester **12** to give acyl ammonium

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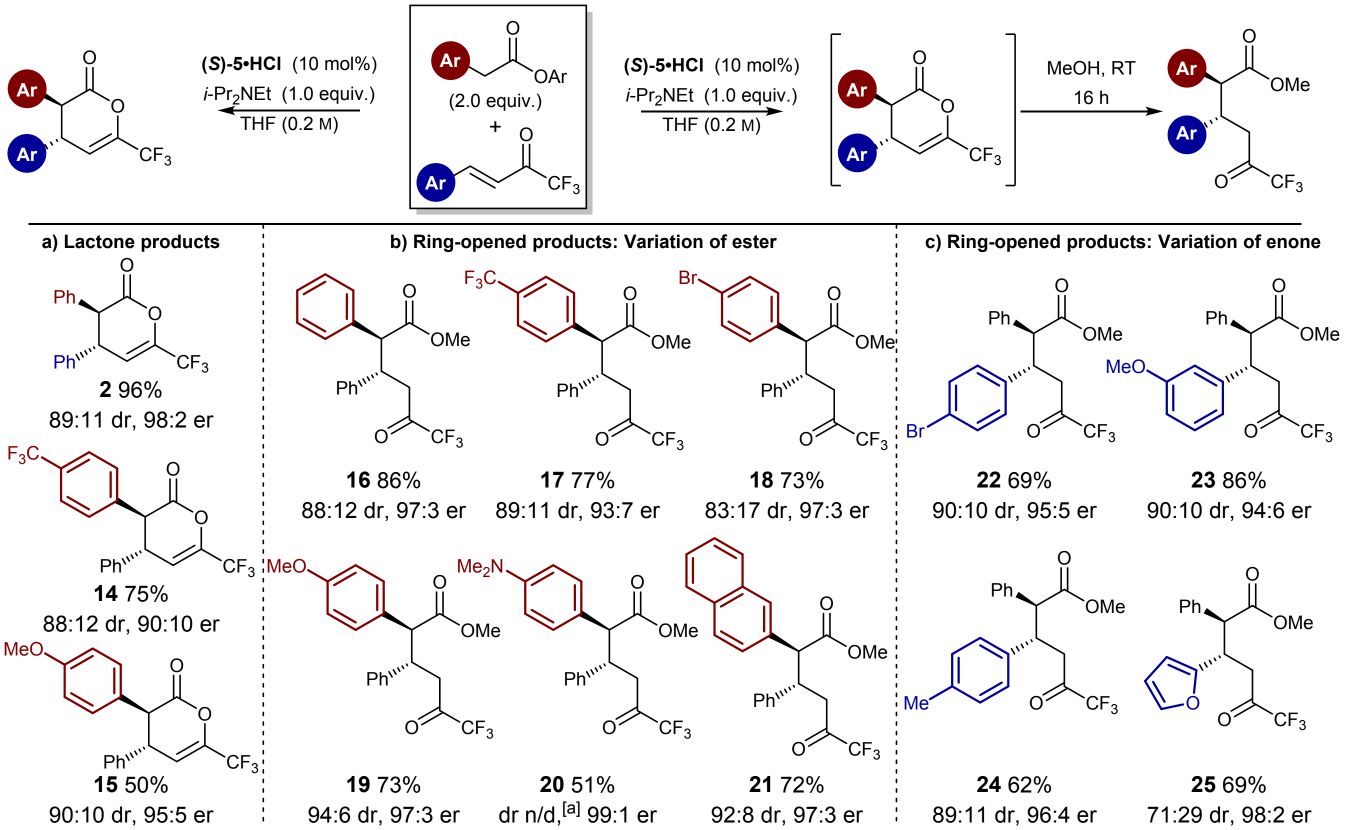
Table 3: Substrate screen.



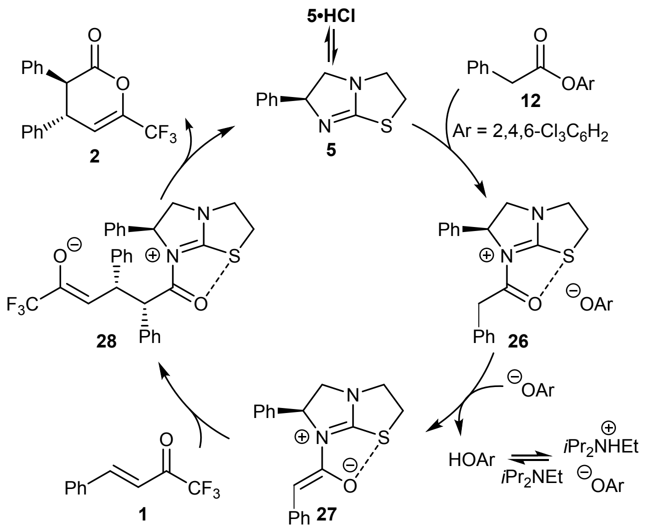
Yields are the isolated yield for a mixture of diastereoisomers after purification. The reported dr is that of the crude material as determined by ^{1}H NMR spectroscopic analysis. The reported er is given for the major diastereomer (3*S*,4*S*):(3*R*,4*R*) as determined by chiral HPLC analysis. [a] dr could not be determined by ^{1}H NMR spectroscopic analysis of the crude material. dr of isolated **19** was 81:18.

ion pair **26**.[5] Deprotonation by the aryloxide counter ion then gives the favoured (*Z*)-ammonium enolate intermediate **27**, which exhibits a *syn*-coplanar geometry due to a stabilising O···S interaction.[22] Ammonium enolate **27** stereoselectively reacts with enone **1** to give intermediate **28**. Subsequent cyclisation gives dihydropyranone **2** and regenerates catalyst **5**.

Conclusions

In conclusion, electron deficient aryl esters are efficient ammonium enolate precursors combining the properties of being competent acylating agents and having a leaving group that is a suitable base for ammonium enolate formation. In a Michael addition-lactonisation with trifluoromethyl enones, trichlorophenyl esters proved to be viable C(1)-ammonium enolate precursors giving dihydropyranone products in good to excellent yield and high enantio- and diastereoselectivity. In contrast to other ammonium enolate precursors such as mixed anhydrides, symmetric anhydrides or acyl imidazoles, tetramisole **5·HCl** proved to be the optimal isothiourea catalyst. Subsequent in situ ring opening of dihydropyranones with methanol led to a range of highly functionalised keto-esters in moderate to excellent yield and up to excellent enantio- and diastereoselectivity.

Scheme 1: Proposed catalytic cycle.



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Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013) ERC Grant Agreement no. 279850 (CMY, JET). ADS thanks the Royal Society for a Wolfson Merit Award. We also thank the EPSRC UK National Mass Spectrometry Facility at Swansea University.

Notes and references

1 For reviews of ammonium enolates see: a) M. J. Gaunt and C. C. Johansson, *Chem. Rev.*, 2007, **107**, 5596; b) K. N. Van, L. C. Morrill, A. D. Smith and D. Romo in *Lewis Base Catalysis in Organic Synthesis*, ed.: E. Vedejs and S. E. Denmark, Wiley, Hoboken, vol. 2, ch. 13, pp.527.
2 For selected examples see: a) R. Samtle and H. Pracejus, *J. Prakt. Chem*., 1972, **314**, 157; b) J. C. Sauer, *J. Am. Chem. Soc.*, 1947, **69**, 2444; c) H. Wynberg and E. G. J. Staring, *J. Am. Chem. Soc.*, 1982, **104**, 166.
3 a) For reviews, see: L. C. Morrill and A. D. Smith, *Chem. Soc. Rev.*, 2014, **43**, 6214; b) J. Merad, J.-M. Pons, O. Chuzel and C. Bressy, *Eur. J. Org. Chem*., 2016, **2016**, 5589.
4 For selected examples see: a) V. C. Purohit, A. S. Malta and D. Romo, *J. Am. Chem. Soc*., 2008, **130**, 10478; b) C. A. Leverett, V. C. Purohit and D. Romo, *Angew. Chem. Int. Ed.,* **49**, 2010, 9479; c) D. Belmessieri, L. C. Morrill, C. Simal, A. M. Z. Slawin and A. D. Smith, *J. Am. Chem. Soc.,* 2011, **133**, 2714; d) D. Belmessieri, D. B. Cordes, A. M. Z. Slawin and A. D. Smith, *Org. Lett.*, 2013, **15**, 3472; e) S. R. Smith, J. Douglas, H. Prevet, P. Shapland, A. M. Z. Slawin and A. D. Smith, *J. Org. Chem.,* 2014, **79**, 1626.
5 L. C. Morrill, J. Douglas, T. Lebl, A. M. Z. Slawin, D. J. Fox and A. D. Smith, *Chem. Sci.*, 2013, **4**, 4146.
6 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.
7 C. M. Young, D. G. Stark, T. H. West, J. E. Taylor and A. D. Smith, *Angew. Chem. Int. Ed.*, 2016, **55**, 14394.
8 For selected examples, see: a) K. Nakata, K. Gotoh, K. Ono, K. Futami and I. Shiina, *Org. Lett*., 2013, **15**, 1170; b) T. H. West, D. M. Walden, J. E. Taylor, A. C. Brueckner, R. C. Johnson, P. H.-Y. Cheong, G. C. Lloyd-Jones and A. D. Smith, *J. Am. Chem. Soc.*, 2017, **139**, 4366.
9 J. E. Taylor and S. D. Bull, in *Comprehensive Organic Synthesis II*, ed.: P. Knochel, Elsevier, Amsterdam, *2nd edn*, 2014, vol. 6, pp. 427.
10 a) L. Hao, X. Chen, S. Chen, K. Jiang, J. Torres and Y. R. Chi, *Org. Chem. Front.*, 2014, **1**, 148; b) L. Hao, Y. Du, H. Lv, X. Chen, H. Jiang, Y. Shao and Y. R. Chi, *Org. Lett.,* 2012, **14**, 2154.
11 A. Matviitsuk, J. E. Taylor, D. B. Cordes, A. M. Z. Slawin and A. D. Smith, *Chem. Eur. J.*, 2016, **22**, 17748.
12 For a review see: W. C. Hartley, T. J. C. O'Riordan and A. D. Smith, *Synthesis*, 2017, **49**, 3303.
13 a) T. H. West, D. S. B. Daniels, A. M. Z. Slawin and A. D. Smith, *J. Am. Chem. Soc.*, 2014, **136**, 4476; b) T. H. West, S. S. M. Spoehrle and A. D. Smith, *Tetrahedron*, 2017, **73**, 4138; c) S. S. M. Spoerhle, T. H. West, J. E. Taylor, A. M. Z. Slawin and A. D. Smith, *J. Am. Chem. Soc.*, 2017, **139**, 11895; d) K. Kasten, A. M. Z. Slawin and A. D. Smith, *Org. Lett.*, 2017, **19**, 5182.
14 J. N. Arokianathar, A. B. Frost, A. M. Z. Slawin, D. Stead and A. D. Smith, *ACS Catalysis*, 2018, **8**, 1153.
15 A. Matviitsuk, M. D. Greenhalgh, D. -J. Barrios Antúnez, A. M. Z. Slawin and A. D. Smith, *Angew. Chem. Int. Ed.*, 2017, **56**, 12282.
16 a) K. J. Schwarz, J. L. Amos, J. C. Klein, D. T. Do and T. N. Snaddon, *J. Am. Chem. Soc*., 2016, **138**, 5214; b) K. J. Schwarz, C. M. Pearson, G. A. Contron-Rosada, P. Liu and T. N. Snaddon, *Angew. Chem. Int. Ed*, 2018, **57**, 7800; c) K. J. Schwarz, C. Yang, J. W. B. Fyfe and T. N. Snaddon, *Angew. Chem. Int. Ed*, 2018, **57**, 12102; d) L. Hutchings-Goetz, C. Yang and T. N. Snaddon, *ACS Catal*., 2018, **8**, 10537; e) W. R. Scaggs and T. N. Snaddon, *Chem. Eur. J.* 2018, **24**, 14378; f) J. W. B. Fyfe, O. M. Kabia, C. M. Pearson and T. N. Snaddon, *Tetrahedron*, 2018, **74**, 5383; g). W. R. Scaggs, T. D. Scaggs and T. N. Snaddon, *Org. Biomol. Chem.*, 2019, **17***,* 1787.
17 X. Jiang; J. J. Beiger and J. F. Hartwig, *J. Am. Chem. Soc.*, 2017, **139**, 87.
18 Aryl esters have been used in formal [3+2] cycloadditions: J. Song, Z. -J. Zhang, S. -S. Chen, T. Fan and L. -Z. Gong, *J. Am. Chem. Soc.*, 2018, **140**, 3177
19 Relative and absolute product configurations assigned by reference to previous work[5]
20 M. D. Greenhalgh, S. Qu, A. M. Z. Slawin and A. D. Smith, *Chem. Sci*., 2018, **9**, 4909.
21 For full details see Supporting Information.
22 a) V. I. Minkin and R. M. Minyaev, *Chem. Rev.* 2001, **101**, 1247; b) Y. Nagao, T. Hirata, S Goto, S. Sano and A. Kakehi, *J. Am. Chem. Soc*., 1998, **120**, 3104; c) V. Birman, X. Li and Z. Han *Org. Lett.,* 2007, **9**, 37 d) K. A. Brameld, B. Kuhn, D. C. Reuter and M. Stahl, *J. Chem. Inf. Model*. 2008, **48**, 1; e) P. Liu, X. Yang, V. B. Birman and K. N. Houk, *Org. Lett*. 2012, **14**, 3288; f) E. R. T. Robinson, D. M. Walden, C. Fallan, M. D. Geenhalgh, P. H. -Y. Cheong and A. D. Smith, *Chem. Sci.,* 2016, **7**, 6919 g) D. J. Pascoe, K. B. Ling and S. L. Cockroft, *J. Am. Chem. Soc.*, 2017, **139**, 15160 h) M. D. Greenhalgh, S. M. Smith, D. M. Walden, J. E. Taylor, Z. Brice, E. R. T. Robinson, C. Fallan, D. B. Cordes, A. M. Z. Slawin, H. C. Richardson, M. A. Grove, P. H. -Y. Cheong and A. D. Smith. *Angew. Chem. Int. Ed.,* 2016, **7**, 6919
23 The data underpinning this research can be found at DOI: https://doi.org/10.17630/cb133261-b58e-4d72-b380-c877c993dc5d