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α-Ketophosphonates as Ester Surrogates: Isothiourea-Catalyzed Asymmetric Diester and Lactone Synthesis

Siobhan R. Smith,[†] Stuart M. Leckie,[†] Reuben Holmes,[†] James Douglas,[†] Charlene Fallan,[†] Peter Shapland,[‡] David Pryde,[§] Alexandra M. Z. Slawin,[†] and Andrew D. Smith*[,†]

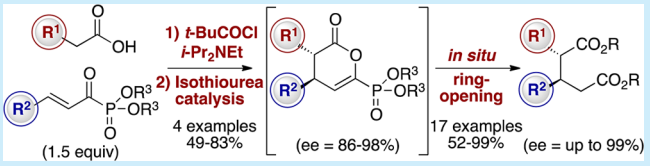
[†]EaStCHEM, School of Chemistry, University of St. Andrews, North Haugh, St. Andrews KY16 9ST, U.K.

[‡]GSK, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, U.K.

[§]Pfizer Neusentis, The Portway Building, Granta Park, Great Abington, Cambridge CB21 6GS, U.K.

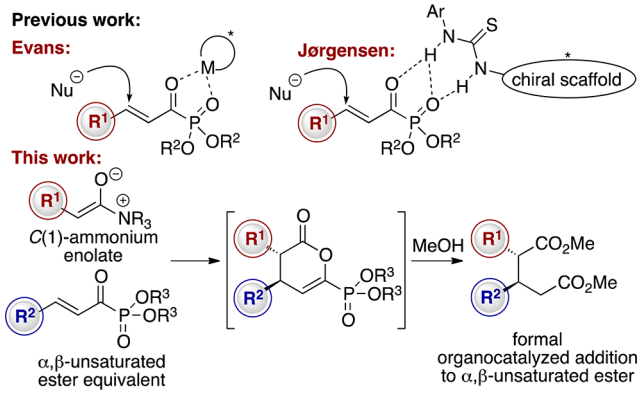
Supporting Information

ABSTRACT: Isothiourea HBTM-2.1 catalyzes the asymmetric Michael addition/lactonization of aryl- and alkenylacetic acids using α-keto-β,γ-unsaturated phosphonates as α,β-unsaturated ester surrogates, giving access to a diverse range of stereodefined lactones or enantioenriched functionalized diesters upon ring-opening.



Lewis base organocatalysis has developed as a powerful tool for the enantioselective construction of carbon−carbon bonds.[1] Within this area, the asymmetric addition of enolates and their derivatives via the use of cinchona alkaloids,[2] enamines,[3] and azolium enolates[4] generated with N-heterocyclic carbenes (NHCs)[5] to electron-deficient alkenes has received widespread attention in recent years. Catalytic asymmetric conjugate additions employing enones and enals is well established,[6] although the use of α,β-unsaturated esters and amides remains challenging due to the intrinsic decreased reactivity of these motifs. Efforts to circumvent this issue have used *N*-acylpyrroles,[7] 2-acylimidazoles,[8] and activated imides[9] as ester surrogates, while Evans[10] and Jørgensen[11] have pioneered the use of α-keto-β,γ-unsaturated phosphonates as ester equivalents. Using transition metal and organocatalysts, respectively, these methods activate the α-ketophosphonate for nucleophilic attack via bidentate coordination of a Lewis acid or hydrogen bonding to a thiourea catalyst architecture (Scheme 1).

Scheme 1. Initial Concept



Building on Romo's pioneering nucleophile-catalyzed aldol lactonization (NCAL) strategy,[12] we have previously studied the isothiourea[13]-catalyzed asymmetric functionalization of carboxylic acids[14] via ammonium enolates.[15] This process requires highly electron-deficient alkene components in Michael−lactonization reactions, with α,β-unsaturated esters inert to typical reaction conditions. This manuscript explores α-ketophosphonates as α,β-unsaturated ester equivalents,[16] affording stereodefined diesters upon ring-opening that are suitable for further synthetic manipulations.

Initial investigations employed phenylacetic acid **1** and α-ketophosphonate **2** in a model system and assessed a range of isothiourea Lewis base catalysts (**5**−**7**, Table 1). In situ formation of the mixed anhydride with pivaloyl chloride and *i*-Pr_2NEt, followed by treatment with isothiourea **5**, gave *anti*-lactone **3** in 66% isolated yield with modest ee (entry 1). A screen of isothioureas revealed HBTM-2.1 **7** as the optimum catalyst, providing lactone **3** in 86% ee (entry 3). This catalyst was then examined using toluene and THF as the solvent, affording decreased isolated yields but with high diastereocontrol (entries 4 and 5). Lowering the temperature to −78 °C (entry 6) led to improved isolated yield, dr, and ee. Gratifyingly, a catalyst loading of only 1 mol % at −78 °C gave the product in good yield with excellent stereocontrol (entry 7). Finally, in situ methanolysis of lactone **3** gave diester **4** and provided proof of principle that α-ketophosphonates act as ester surrogates in this system (entry 8).

The scope and limitations of this process were next probed, initially to generate a small range of stereodefined lactones (Table 2, conditions A). Pleasingly, both electron-rich and electron-deficient arylacetic acids were suitable ammonium enolate precursors, and the functionalized lactones (**3**, **8**−**10**)

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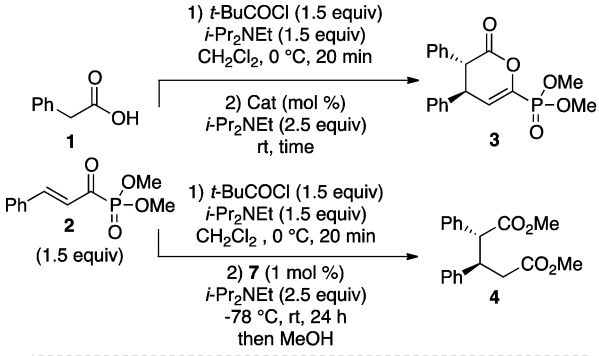
Table 1. Optimization



entry	catalyst (mol %)	product	time (h)	yield[a] (%)	dr[b]	ee[c] (%)
1	**5** (10)	**3**	2	66	84:16	60 (*ent*)
2	**6** (10)	**3**	1	39	74:26	56
3	**7** (10)	**3**	1	51	88:12	86
4[d]	**7** (10)	**3**	2	41	89:11	97
5[e]	**7** (10)	**3**	24	10	87:13	62
6[f]	**7** (10)	**3**	24	67	90:10	98
7[f]	**7** (1)	**3**	24	83	>95:5	98
8	**7** (1)	**4**	24	63	92:8	97

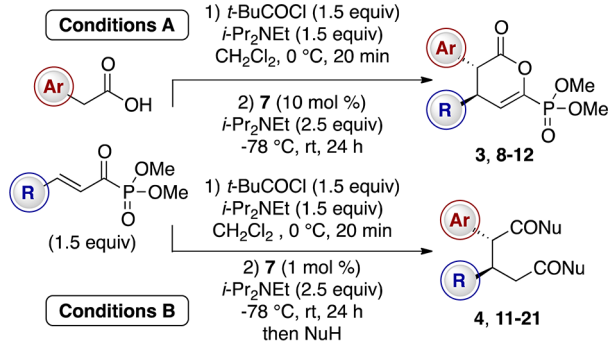
[a]Isolated yield of product following chromatography. [b]Determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c]Determined by chiral HPLC analysis. [d]Reaction in toluene. [e]Reaction in THF. [f]Reaction at −78 °C.

were isolated following Lewis base catalysis in good yield with high diastereo- and enantiocontrol. The ability of the phosphonate group to act as a masked ester/amide equivalent was assessed with a range of arylacetic acids and α-ketophosphonates using a low catalyst loading of 1 mol %. The lactones were ring-opened in situ with a range of nucleophiles to reveal 1,5-diester or-diamide products (Table 2, conditions B) in high yield with excellent stereocontrol. Arylacetic acids containing both electron-withdrawing and electron-donating substituents in the *meta* and *para* positions were incorporated in high yield while maintaining excellent levels of enantio- and diastereoselectivity (**4**, **11**−**21**).[17] Extended aromatic systems were also well tolerated (**16**). Additionally, α-ketophosphonates containing electron-rich and electron-deficient aromatic substitution were competent in this process (**17** and **18**), and significantly, aliphatic substitution was also tolerated with good isolated yield and high levels of selectivity (**19**). Finally, allyl alcohol and *i*-PrNH$_2$ were employed in lactone ring-opening, providing diester **20** and diamide **21**, respectively, in excellent yields, with high enantio- and diastereocontrol.

Single-crystal X-ray structure analysis of diester **15** allowed unambiguous determination of the relative and absolute configuration as (2*R*,3*R*) (Figure 1).[18] All other diesters within this series were assigned by analogy.

Variation of the α-ketophosphonate was also explored using isopropyl phosphonate **22** (Table 3). The improved preparation and isolation of **22**,[19] in addition to its increased bench stability over methyl phosphonate **2**, allowed further examina-

Table 2. Reaction Scope



product yield %[a]	dr[b] (ee)[c]	product yield %[a]	dr[b] (ee)[c]
(A) **3**,[d] 83%	>95:5 (98%)	**8**, 49%	92:8 (97%)
9, 54%	91:9 (86%)	**10**, 62%	92:8 (98%)
(B) **4**, 63%	92:8 (97%)	**11**, 52%	93:7 (87%)
12, 56%	93:7 (>99%)	**13**, 78%	94:6 (99%)
14, 70%	91:9 (98%)	**15**, 78%	92:8 (92%)
16, 67%	94:6 (98%)	**17**, 58%	94:6 (99%)
18, 99%	90:10 (98%)	**19**, 55%	88:12 (97%)
20, 79%	93:7 (92%)	**21**, 76%	91:9 (99%)

[a]Isolated yield of product following chromatography. [b]Determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c]Determined by chiral HPLC analysis. [d]1 mol % of catalyst **7** employed.

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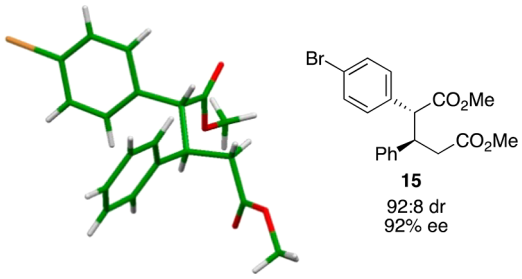
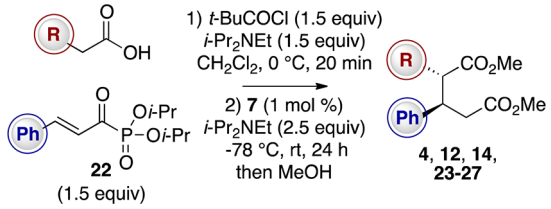
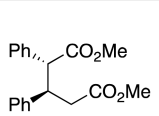
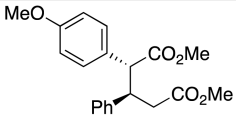
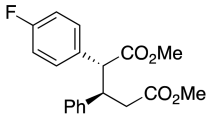
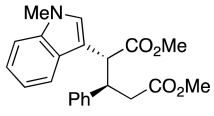
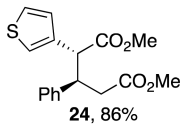
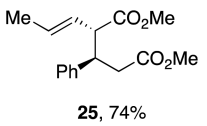
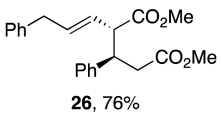
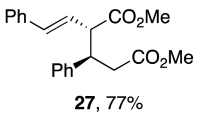


Figure 1. Representation of the single-crystal X-ray structure of diester **15**.

Table 3. Substrate Scope Using Isopropyl Phosphonate 22



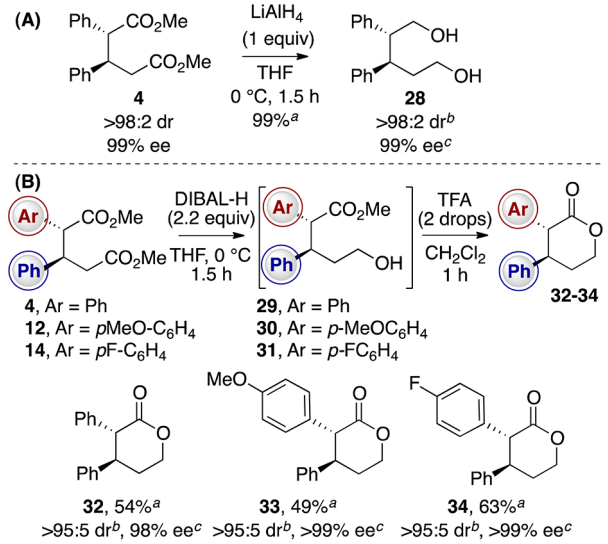
product yield %[a]	dr[b] (ee)[c]	product yield %[a]	dr[b] (ee)[c]
 **4**, 87% 5 mmol scale	>95:5 (98%)	 **12**, 73%	>95:5 (>99%)
 **14**, 77%	85:15 (99%)	 **23**, 62%	86:14 (88%)
 **24**, 86%	>95:5 (>99%)	 **25**, 74%	>95:5 (>99%)
 **26**, 76%	>95:5 (>99%)	 **27**, 77%	>95:5 (27%)

[a]Isolated yield of product following chromatography. [b]Determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c]Determined by chiral HPLC analysis.

tion of the substrate scope in this process. Using phosphonate **22**, this methodology was amenable to large-scale synthesis, and diester **4** was obtained in 87% isolated yield (0.95 g, 5 mmol scale) with excellent stereocontrol. Again, a range of diester products using arylacetic acids were synthesized in excellent isolated yields, with high diastereo- and enantiocontrol (**12** and **14**). Notably, the substrate scope was expanded to include heteroarylacetic and alkenylacetic acids, giving functionalized diesters **23**–**27** in high yield. However, the styrene **27** was isolated with diminished levels of enantiocontrol (27% ee).

To demonstrate the potential utility of this methodology, synthetic transformations of the diester products were investigated. First, complete reduction of the diester functionality was achieved by treating **4** with $LiAlH_4$ (1 equiv) in THF at 0 °C, giving diol **28** in quantitative yield and 99% ee (Scheme 2A). Additionally, selective reduction of the least

Scheme 2. Derivatizations

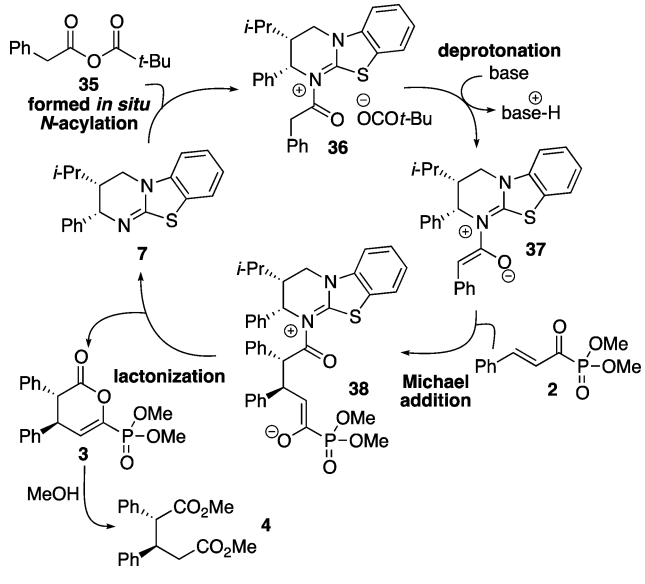


[a]Isolated yield of product following chromatography. [b]Determined by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c]Determined by chiral HPLC analysis.

hindered ester in **4**, **12**, and **14** was achieved by careful control of reaction conditions with DIBAL-H (2.2 equiv) in THF at 0 °C giving alcohols **29**–**31**, respectively.[20] Subsequent acid-catalyzed lactonization of **29**–**31** was achieved with TFA giving the enantiomerically enriched lactones **32**–**34** in good yield over two steps (Scheme 2B).[21] Such aryl-substituted δ-lactones are of medicinal and synthetic interest.[22]

The proposed mechanism of the process begins with *N*-acylation of HBTM-2.1 **7** with mixed anhydride **35** formed in situ (Scheme 3). Subsequent deprotonation of **36** generates (*Z*)-ammonium enolate **37**, which undergoes Michael addition to α-ketophosphonate **2**. Lactonization regenerates the

Scheme 3. Proposed Mechanism



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isothiourea catalyst and delivers lactone **3**, which can be ring-opened in situ to afford diester **4**.

In conclusion, we have demonstrated the Michael addition/lactonization of a range of acetic acids with α-keto-β,γ-unsaturated phosphonates as masked α,β-unsaturated ester equivalents. The synthetic utility of the lactone and diester products has been demonstrated through a variety of product manipulations, affording a range of stereodefined building blocks. Further studies within our laboratory are directed toward the development of isothioureas in catalysis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral and HPLC data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ads10@st-andrews.ac.uk.

Notes

The authors declare no competing financial interest.

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(16) Methyl cinnamate is not a competent electrophile for this process. For a recent example of β,γ-unsaturated α-ketophosphonates in NHC catalysis, see: Leckie, S. M.; Fallan, C.; Taylor, J. E.; Brown, T. B.; Pryde, D.; Lébl, T.; Slawin, A. M. Z.; Smith, A. D. *Synlett* **2013**, *24*, 1243−1249.

(17) *Ortho* substituents on the arylacetic acid were not tolerated in this process under a range of reaction conditions.

(18) CCDC 980638 contains the supplementary crystallographic data for **15**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(19) See the Supporting Information for details.

(20) Alcohol **29** was isolated in 91% yield from the reduction of diester **4** with retention of stereochemistry. See the Supporting Information for details.

(21) Lactone **32** was also obtained in quantitative yield from isolated alcohol **29**. See the Supporting Information for details.

(22) For example, see: Smitrovich, J. H.; Boice, G. N.; Qu, C.; DiMichele, L.; Nelson, T. D.; Huffman, M. A.; Murry, J.; McNamara, J.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1963−1966.