

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

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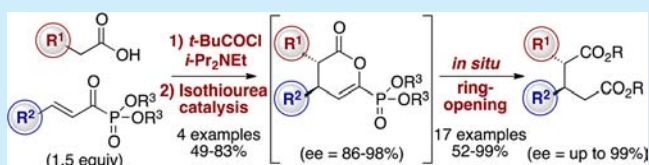
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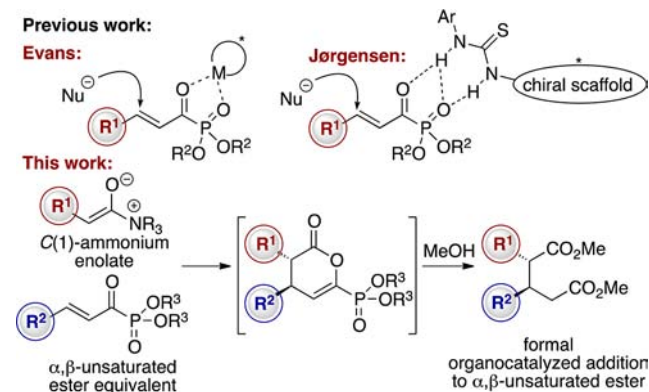
S Supporting Information

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 enolates⁴ 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 imides⁹ as ester surrogates, while Evans¹⁰ and Jørgensen¹¹ 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 isothiourea¹³-catalyzed asymmetric functionalization of carboxylic acids¹⁴ 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.

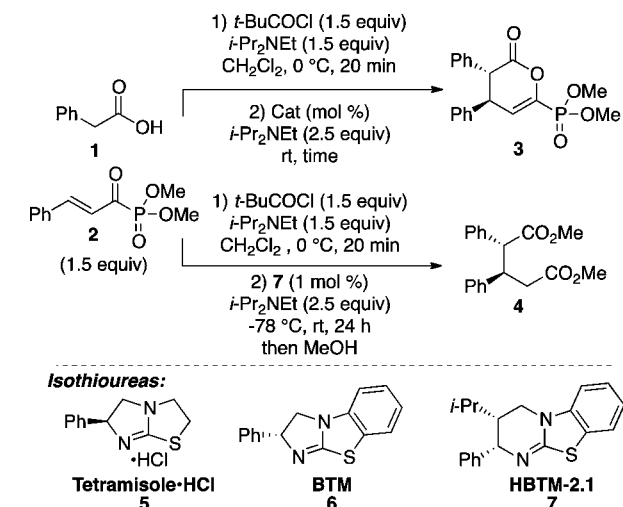
Initial investigations employed phenylacetic acid **1** and α -ketophosphonate **2** in a model system and assessed a range of isothiourea Lewis base catalysts (**5**–**7**, Table 1). In situ formation of the mixed anhydride with pivaloyl chloride and *i*-Pr₂NEt, followed by treatment with isothiourea **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 diastereoselectivity (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

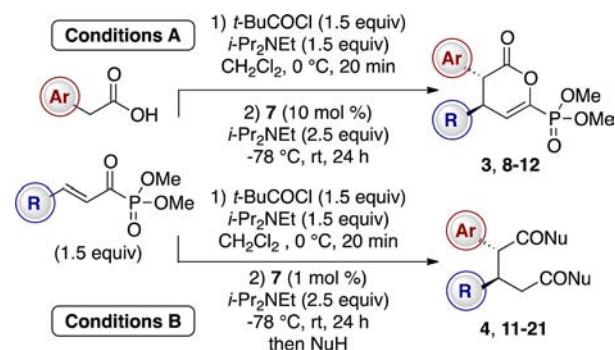
^aIsolated yield of product following chromatography. ^bDetermined by ¹H NMR spectroscopic analysis of the unpurified reaction mixture. ^cDetermined by chiral HPLC analysis. ^dReaction in toluene. ^eReaction in THF. ^fReaction at -78°C .

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*-PrNH₂ 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	dr ^b	product	dr ^b
yield % ^a	(ee) ^c	yield % ^a	(ee) ^c
(A)	>95:5 (98%)		92:8 (97%)
3, ^d 83%		8, 49%	
	91:9 (86%)		92:8 (98%)
9, 54%		10, 62%	
(B)	92:8 (97%)		93:7 (87%)
4, 63%		11, 52%	
	93:7 (>99%)		94:6 (99%)
12, 56%		13, 78%	
	91:9 (98%)		92:8 (92%)
14, 70%		15, 78%	
	94:6 (98%)		94:6 (99%)
16, 67%		17, 58%	
	90:10 (98%)		88:12 (97%)
18, 99%		19, 55%	
	93:7 (92%)		91:9 (99%)
20, 79%		21, 76%	

^aIsolated yield of product following chromatography. ^bDetermined by ¹H NMR spectroscopic analysis of the unpurified reaction mixture. ^cDetermined by chiral HPLC analysis. ^d1 mol % of catalyst 7 employed.

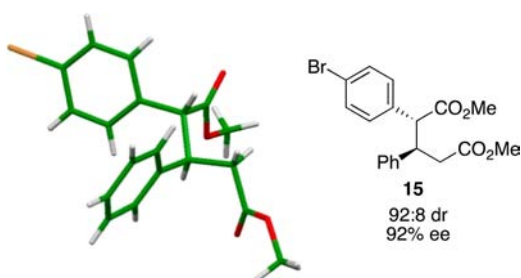
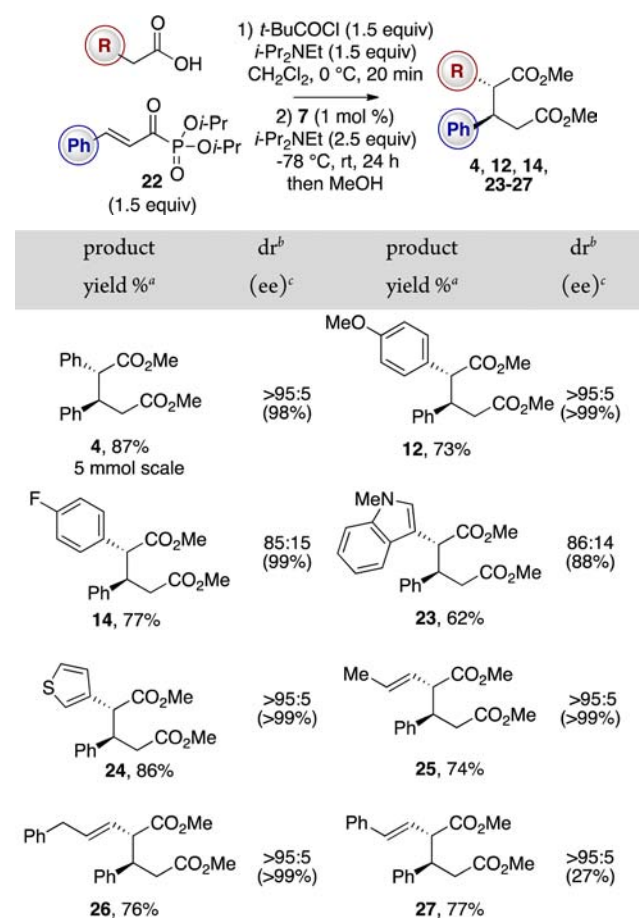


Figure 1. Representation of the single-crystal X-ray structure of diester 15.

Table 3. Substrate Scope Using Isopropyl Phosphonate 22



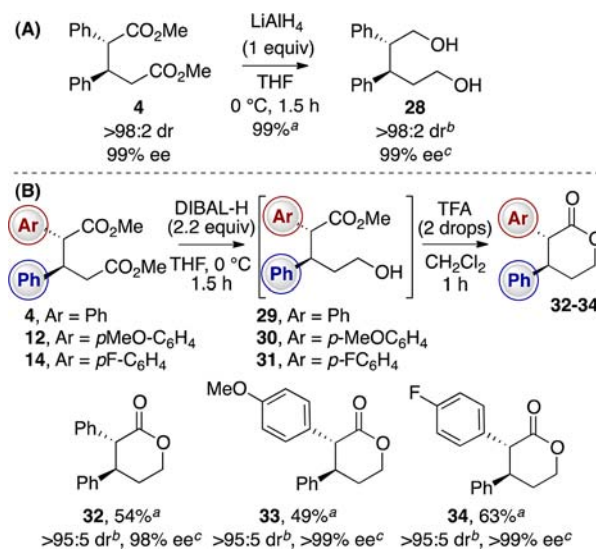
^aIsolated yield of product following chromatography. ^bDetermined by ¹H NMR spectroscopic analysis of the unpurified reaction mixture. ^cDetermined by chiral HPLC analysis.

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 function-

ality was achieved by treating 4 with LiAlH₄ (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

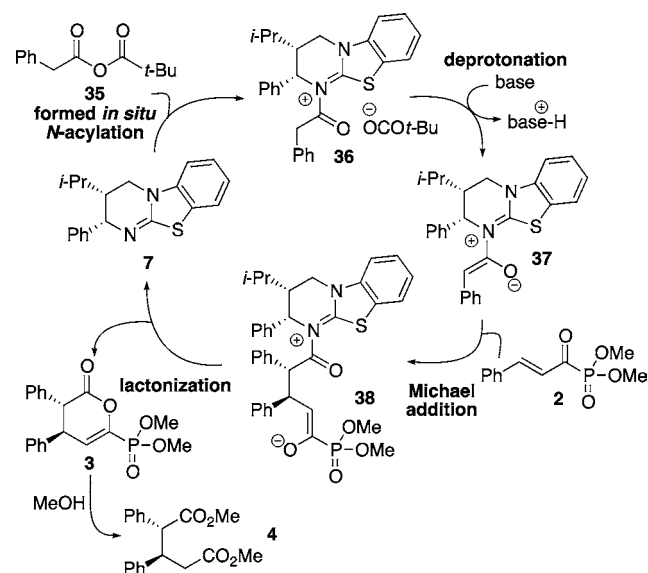


^aIsolated yield of product following chromatography. ^bDetermined by ¹H NMR spectroscopic analysis of the unpurified reaction mixture. ^cDetermined by chiral HPLC analysis.

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



isothioureia 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 isothiureas 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>.

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Notes

The authors declare no competing financial interest.

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(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.

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