

Cite this: *Chem. Sci.*, 2025, 16, 6828

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 14th January 2025
Accepted 5th March 2025

DOI: 10.1039/d5sc00322a

rsc.li/chemical-science

Isothiourea-catalysed enantioselective synthesis of phosphonate-functionalised β -lactones†

Ffion M. Platt,[‡] Yihong Wang,[‡] David B. Cordes,[‡] Aidan P. McKay,^a Alexandra M. Z. Slawin,[‡] Heena Panchal^b and Andrew D. Smith^{‡*}

Despite growing interest in the reactivity and biological activity of phosphonate-containing molecules, the application of α -ketophosphonates in enantioselective formal [2 + 2] cycloadditions to generate β -lactones bearing a pendant phosphonate group remains unreported. In this manuscript, a highly diastereo- and enantioselective isothiourea-catalysed formal [2 + 2] cycloaddition of both alkyl- and aryl substituted C(1)-ammonium enolates and α -ketophosphonates is established. This strategy allows a mild, practical and scalable approach to highly enantioenriched C(3)-unsubstituted and C(3)-alkyl β -lactones bearing a phosphonate motif from their corresponding α -silyl acids, *via* a desilylative pathway (30 examples, up to 98%, >95 : 5 dr, >99 : 1 er). Alternatively, the use of (hetero)arylacetic acids allows the preparation of C(3)-(hetero)aryl β -lactones to be accessed in high yields and stereocontrol (19 examples, up to 98%, >95 : 5 dr, 99 : 1 er).

Introduction

Over the last two decades, heterocyclic molecules containing a phosphonic acid or related organophosphorus derivative have drawn broad interest due to their versatile properties and widespread biological activities, finding use as medicines, herbicides, optoelectronic materials and flame retardants.^{1–4} Representative examples include the broad-spectrum antibiotic fosfomycin, the herbicide glyphosate and optoelectronic material benzo[*b*]phospholoxide (Fig. 1a).^{1–3} Given the significant interest in these functionalities, a number of catalytic, enantioselective processes have been developed to generate stereo-defined products bearing the phosphonate functionality *via* the use of α -ketophosphonates.^{5–11} In the same vein, β -lactones are versatile motifs which are prevalent in medicinal chemistry both as synthetic building blocks and as warheads in several biologically active compounds (Fig. 1a).¹² Consequently, many enantioselective protocols exist for their synthesis,^{13–16} among which the use of C(1)-ammonium enolates generated from chiral tertiary amines (including the use of cinchona alkaloids, planar chiral DMAP derivatives and isothioureas) have been widely reported.¹⁷

C(1)-ammonium enolates are powerful reactive intermediates that have been harnessed for enantioselective C–C and C–X bond formation with a broad range of electrophiles. Classically, catalyst turnover occurred through intramolecular cyclisation to afford lactone or lactam products, however intermolecular turnover can be provided using electron-poor phenoxides, which has significantly broadened the scope of electrophiles compatible with this approach.^{18–20} Despite being widely applied, until recently intermolecular reactions with electrophiles involving C(1)-ammonium enolate formation from carboxylic acid starting materials using isothiourea catalysts (such as HyperBTM **1**) was limited to (hetero)aryl-acetic acid derivatives. This presumably reflects the acidity of the α -C–H bond within an intermediate acyl ammonium ion pair for deprotonation to occur (Fig. 1b). To broaden the utility of C(1)-ammonium enolate reactivity to alkyl-substituted C(1)-ammonium enolates, we recently harnessed a desilylative approach from α -silyl carboxylic acids, expanding the scope of substitution within C(1)-ammonium enolates to include benzyl, alkyl and even acetic acid-derivatives (Fig. 1b).²¹

In previous work, Chi *et al.* demonstrated the enantioselective, NHC-catalysed formal [4 + 2] cycloaddition of α,β -unsaturated aldehydes with α -ketophosphonates in the presence of a stoichiometric oxidant to give 2-pyranylphosphonates (Fig. 1c).²² To the best of our knowledge enantioselective formal [2 + 2] cycloadditions using α -ketophosphonates to access β -lactones with a pendant phosphonate group remain unexplored to date. Building on these precedents, we describe a mild and highly enantioselective organocatalytic formal [2 + 2] cycloaddition of both alkyl C(1)-ammonium enolates (formed *via* a desilylative pathway) and (hetero)aryl C(1)-ammonium

^aEaStCHEM, School of Chemistry, University of St Andrews, St Andrews, Fife, KY16 9ST, UK. E-mail: ads10@st-andrews.ac.uk

^bChemical Development, PT&D, AstraZeneca, Etherow Building, Silk Road Business Park, Charter Way, Macclesfield, Cheshire, SK10 2NA, UK

† Electronic supplementary information (ESI) available. CCDC 2395570–2395572. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d5sc00322a>

‡ F. M. Platt and Y. Wang contributed equally to this paper.



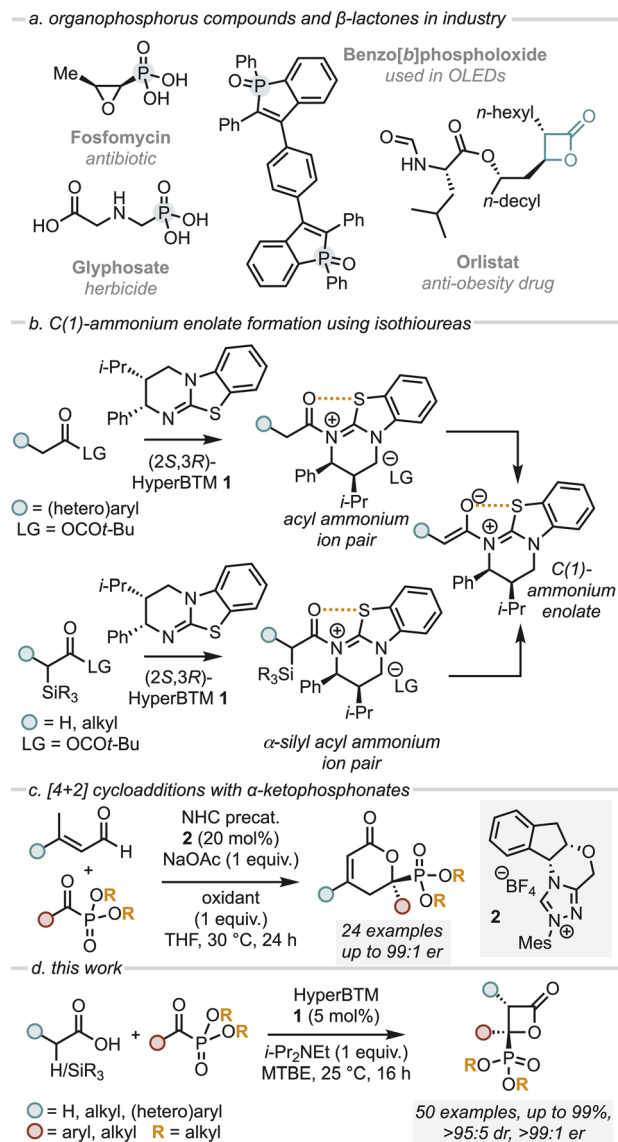


Fig. 1 (a) Importance of organophosphorus compounds; (b) previous methods of generating C(1)-ammonium enolates using isothiourea catalysts; (c) relevant background formal [4 + 2] cycloaddition with α -ketophosphonates; (d) and this work.

enolates (formed by a deprotonation pathway) with a range of α -ketophosphonates using the isothiourea (2*S*,3*R*)-HyperBTM 1 (Fig. 1d). This methodology gives access to a range of stereo-defined β -lactones bearing two stereogenic centres, one of which bears a pendant phosphonate group, in excellent stereoselectivity.

Results and discussion

Investigation of optimal reaction conditions: reactivity of alkyl substituted C(1)-ammonium enolates by desilylation

Using α -trimethylsilyl propionic acid 3 and dimethyl benzoylphosphonate 4 as model substrates, several parameters were screened to find optimal conditions, including acid, catalyst, temperature and solvent (Table 1). Initially, using racemic acid

Table 1 Variation of reaction conditions^a

Entry	Variation from standard	Yield ^b /%	dr ^c	er ^d
1	None	80	>95 : 5	>99 : 1
2	Acid 6	72	>95 : 5	>99 : 1
3	Acid 7	—	—	—
4	Acid 8	—	—	—
5	Propionic anhydride ^e	—	—	—
6	(<i>R</i>)-BTM 9	—	—	—
7	(<i>S</i>)-TM·HCl 10	—	—	—
8	Acid 3 (1 equiv.)	35	>95 : 5	>99 : 1
9	25 °C	98	>95 : 5	>99 : 1
10	CH ₂ Cl ₂ , 25 °C	75	89 : 11	94 : 6
11	CH ₃ CN, 25 °C	78	81 : 19	99 : 1
12	Toluene, 25 °C	80	>95 : 5	>99 : 1
13	THF, 25 °C	25	>95 : 5	79 : 21

^a *t*-BuCOCl (1.2 mmol), *i*-Pr₂NET (1.2 mmol) and acid 3 (0.8 mmol) in MTBE (4 mL, 0.1 M) was stirred at 0 °C for 10 min before the addition of *i*-Pr₂NET (0.4 mmol), α -ketophosphonate 4 (0.4 mmol) and (2*S*,3*R*)-HyperBTM 1 (5 mol%) at 20 °C for 16 h. Temperatures of 25 °C were maintained using an oil bath. MTBE = methyl *tert*-butyl ether. BTM = benztetramisole. TM = tetramisole. ^b Isolated yield. ^c Determined by ¹H NMR of crude reaction mixture. ^d Determined by HPLC analysis on a chiral stationary phase. ^e propionic anhydride (1.0 mmol), *i*-Pr₂NET (0.5 mmol), α -ketophosphonate 4 (0.4 mmol) and (2*S*,3*R*)-HyperBTM 1 (5 mol%) in MTBE (4 mL) at rt for 16 h.

3 (2 equiv.), *t*-BuCOCl (3 equiv.) and *i*-Pr₂NET (3 equiv.) in MTBE to form the mixed anhydride *in situ*, followed by *i*-Pr₂NET (1 equiv.), (2*S*,3*R*)-HyperBTM 1 (5 mol%) and α -ketophosphonate 4 (1 equiv.) at room temperature gave the desired β -lactone 5 in 80% yield with exceptional diastereo- and enantioselectivity (>95 : 5 dr, >99 : 1 er) (entry 1). The use of alternative racemic acid 6 led to reduced yield, albeit with retention of high diastereo- and enantioselectivity (72%, >95 : 5 dr, >99 : 1 er, entry 2), however further variation of the silyl group using racemic acid 7 led to significantly reduced yield (<5%, entry 3). Control reactions showed that the α -silyl-substituent is necessary for reactivity in this process, as the use of propionic acid 8 (for subsequent mixed anhydride formation, entry 4) or propionic anhydride as starting material (entry 5) led to no formation of β -lactone 5. Changing to alternative isothiourea catalysts 9 and 10 led to no reaction (entries 6 and 7) and reducing the stoichiometry of acid 3 led to a reduction in yield, although maintained high stereoselectivity (35%, >95 : 5 dr, entry 8). When the



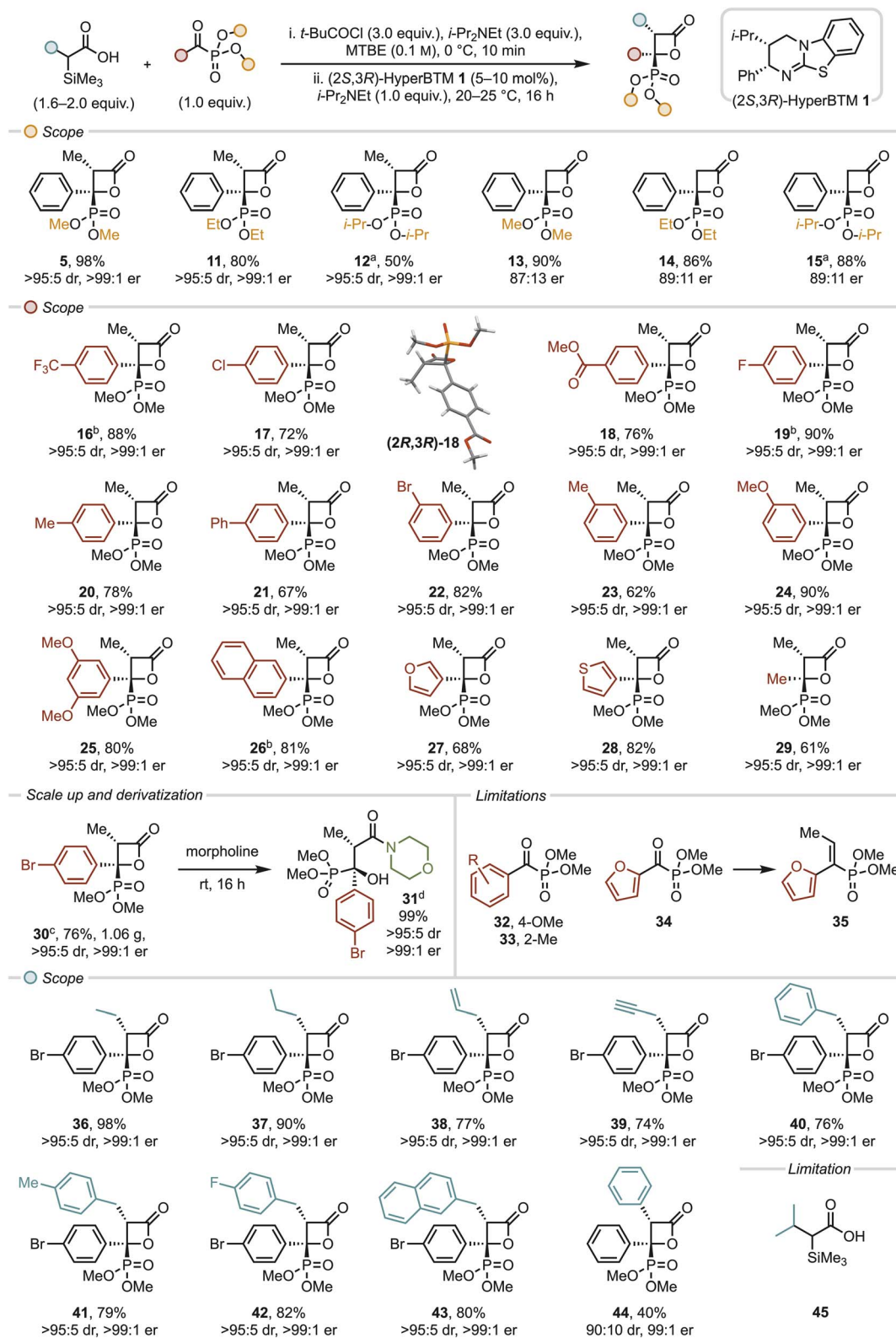


Fig. 2 Scope and limitations of the formal [2 + 2] cycloaddition of α -silyl acids with α -ketophosphonates. All yields are isolated yields, dr determined by ^1H NMR of crude reaction mixture, er determined by HPLC analysis on a chiral stationary phase, reaction scale 0.4 mmol, 25 °C maintained using an oil bath. ^a10 mol% HyperBTM 1 used; ^b1.6 equiv. of acid used, performed at 20 °C; ^cinitial reaction carried out on 0.4 mmol scale, scale up reaction carried out on 4.0 mmol scale, both gave **31** in 76% yield, >95:5 dr, >99:1 er; ^dmorpholine (5.0 equiv.) added after full conversion to β -lactone **31**, 20 °C, 16 h.



temperature was increased to 25 °C (entry 9) β -lactone **5** was obtained in 98% yield, with exceptional stereocontrol (>95 : 5 dr, >99 : 1 er). Variation of the solvent at 25 °C saw no improvement upon these conditions (entries 10–13). Hence, entry 9 was chosen as the optimal reaction conditions.

Scope and limitations

With optimised conditions in hand, the scope and limitations of the developed process were investigated through variation of the phosphonate alkyl group under the standard reaction conditions (Fig. 2). Increasing substitution of the phosphonate group from methyl to ethyl and iso-propyl gave β -lactones **11** and **12** in reduced yield (80% and 50% respectively) compared to **5** but with exceptional stereocontrol (both >95 : 5 dr, >99 : 1 er). Conversely, taking unsubstituted α -silyl acetic acid with α -ketophosphonates of increasing substitution gave C(3)-unsubstituted β -lactones **13–15** in high yields (86–99%) but reduced enantioselectivity (87 : 13–89 : 11 er).

Subsequent work varied the steric and electronic nature of the aryl substituent within the benzoylphosphonate. The incorporation of electron-withdrawing groups in the 4-position were tolerated well, with compounds **16–19** (4-F₃CC₆H₄-, 4-CO₂MeC₆H₄-, 4-ClC₆H₄ and 4-FC₆H₄) prepared in good to high yields (72–90%) with exceptional stereoselectivity (all >95 : 5 dr, >99 : 1 er). Other aryl C(4)-substituents within the benzoylphosphonate were also well-tolerated, giving 4-Me β -lactone **20** and 4-Ph β -lactone **21** in good yields and stereoselectivities (67–78%, both >95 : 5 dr, >99 : 1 er). Further substitution patterns and groups were also compatible, with 3-MeOC₆H₄-, 3-BrC₆H₄-, 3-MeC₆H₄ and 3,5-(MeO)₂C₆H₃ all providing efficient access to the corresponding β -lactones **22–25** with high diastereo- and enantioselectivity (62–90%, all >95 : 5 dr, >99 : 1 er).

Reduced acid stoichiometry (1.6 equiv.) was used with a 2-naphthoylphosphonate, facilitating access to the corresponding β -lactone **26** in 81% yield with exceptional stereoselectivity (>95 : 5 dr, >99 : 1 er). In addition to substituted benzoylphosphonates, heterocyclic α -ketophosphonates were also well-tolerated, providing C(4)-3-furyl and 3-thiophenyl β -lactones **27** and **28** in high yields and stereoselectivities (68–82%, both >95 : 5 dr, >99 : 1 er). Single crystal X-ray diffraction of both **18** and **26** allowed confirmation of their relative and absolute configuration, which is consistent with the stereochemical rationale previously identified within the group for other formal [2 + 2]-cycloadditions using C(1)-ammonium enolates.²³ Pleasingly, when dimethyl acetylphosphonate was employed, β -lactone **29** bearing a C(4)-methyl substituent was formed in 61% yield, with >95 : 5 dr and >99 : 1 er.

The reaction was scaled up, and β -lactone **30** was formed on gram scale with no erosion of stereoselectivity (76%, >95 : 5 dr, >99 : 1 er). Furthermore, treatment of **30** with excess morpholine under ambient conditions provided ring-opened α -hydroxyl- β -amidylphosphonate **31** bearing two contiguous stereocentres in high yield, with no detriment to the diastereo- or enantioselectivity (94%, >95 : 5 dr, >99 : 1 er). The limitations of this protocol were discovered throughout the course of these investigations. Strongly electron-donating groups on the aryl

phosphonate component were not well-tolerated, with for example 4-MeOC₆H₄ substituted α -ketophosphonate **32** leading to less than 5% conversion to the corresponding β -lactone. Furthermore, 2-methylbenzoyl phosphonate **33** was significantly less reactive than its 4-methyl counterpart, leading to <5% conversion of the starting material. While use of 3-furoylphosphonate gave β -lactone **27** in good yield and the product was bench stable, the 2-furoylphosphonate **34** gave no β -lactone product, but instead alkene **35** was obtained in 58% yield, which presumably arises from decarboxylation of the initially formed β -lactone product.²⁴

Further investigations focused on the scope of the α -silyl carboxylic acid. A variety of alkyl (Me, Et), as well as allyl and propargyl groups were well-tolerated, giving the corresponding β -lactones **36–39** in high yields (77–98%) and exceptional diastereo- and enantioselectivity (all >95 : 5 dr, >99 : 1 er). Benzyl-derived acids, including those bearing 4-MeC₆H₄ and 4-FC₆H₄ substituents, also showed excellent reactivity, affording β -lactones **40–42** in good yields (76–82%) with consistently high stereocontrol (all >95 : 5 dr, >99 : 1 er). Furthermore, 3-(naphthalen-2-yl)propanoic acid delivered the corresponding β -lactone **43** in 80% yield, with >95 : 5 dr and >99 : 1 er. The reaction of α -trimethylsilyl phenylacetic acid was also investigated, which provided β -lactone **44** in only a moderate yield and with a noticeable decrease in diastereoselectivity, although high enantioselectivity was maintained (40%, 90 : 10 dr, 99 : 1 er). Disappointingly, branched iso-propyl α -silyl acid **45** showed no reactivity under the reaction conditions.

Probing double stereodifferentiation: matched and mismatched reaction pairings with enantioenriched anhydride

As a control, rather than (\pm)- α -alkyl- α -silyl mixed anhydride, the use of enantioenriched α -silyl acid **6** (89 : 11 er) was investigated upon reaction with the enantiomers of HyperBTM **1** (Fig. 3). Using (2*S*,3*R*)-**1** gave full conversion to (2*R*,3*R*)-**30** within 10 hours in 72% yield and excellent stereocontrol (>95 : 5 dr, >99 : 1 er). However, the use of enantiomeric (2*R*,3*S*)-**1** gave (2*S*,3*S*)-**30** with identical stereocontrol (>95 : 5 dr, >99 : 1 er) but took 20

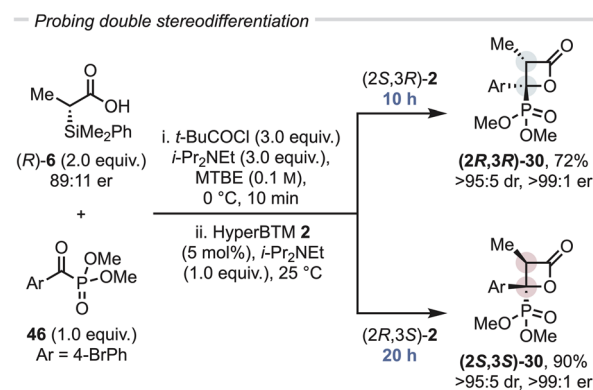


Fig. 3 Probing double stereodifferentiation. All yields are isolated yields, dr determined by ¹H NMR of crude reaction mixture, er determined by HPLC analysis on a chiral stationary phase.



hours to reach completion. This is consistent with the previously observed kinetic resolution of the α -silyl anhydride taking place upon acylation in this protocol.²¹

Re-optimisation of reaction conditions: (hetero)aryl substituted C(1)-ammonium enolates by deprotonation

Since the synthesis of β -lactone **44** from an aryl substituted-silyl acid had proceeded with reduced yield and diastereoselectivity compared to C(3)-alkyl or benzyl substituents, further work considered the propensity for formation of β -lactones bearing a C(3)-aryl substituent *via* a deprotonation route (Table 2). Building upon previous work that demonstrated the ability of phenylacetic anhydrides (either isolated or prepared *in situ*) to act as ammonium enolate precursors,²³ the corresponding pivalic anhydride was prepared *in situ* from phenylacetic acid **47**, with addition of α -ketophosphonate **4** leading to β -lactone **44** in 39% yield, 90 : 10 dr and 98 : 2 er (entry 1). Reducing the equivalents of base in the generation of the mixed pivalic anhydride led to a modest increase in yield, whilst maintaining high stereoselectivity (entry 2). Further variation in stoichiometry (see Tables S7 to S10[†]) led to an optimal ratio of 3 : 3 : 3 of acid **47** : *t*-BuCOCl : *i*-Pr₂NEt. Further optimisation showed that varying the rate of acid had a significant impact on the reaction yield (entries 3–6), with addition of the acid over 5 min optimal, giving β -lactone **44** in an isolated yield of 74% with 90 : 10 dr and 96 : 4 er.

Probing *in situ* epimerisation of C(3)-aryl β -lactones under reaction conditions

During the optimisation of this reaction, significant variation in product diastereoselectivity was observed and it was considered

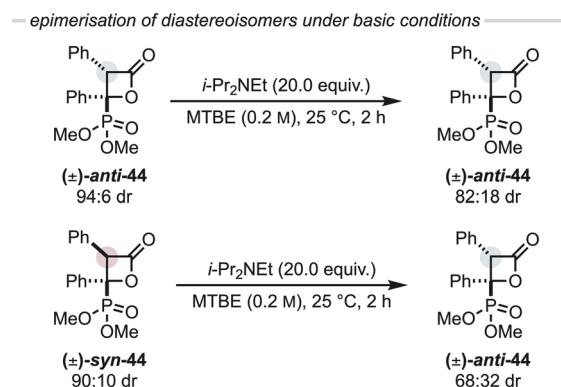


Fig. 4 Epimerisation studies.

that this may be due to epimerisation of the β -lactone product. To evaluate the potential epimerisation of β -lactone **44** under the reaction conditions, isolated diastereomerically enriched samples of (\pm)-*anti*- and (\pm)-*syn*-**44** (94 : 6 and 10 : 90 dr_{*anti:syn*} respectively) were exposed to *i*-Pr₂NEt (20.0 equiv.) in MTBE, at 25 °C for 2 h (Fig. 4). After this time the diastereomeric ratio of *anti*-**44** was reduced from 94 : 6 to 82 : 18 dr_{*anti:syn*}, while *anti*-**44** (68 : 32 dr_{*anti:syn*}) was also favoured starting from *syn*- β -lactone **44** (90 : 10 dr_{*syn:anti*}). Consistent with previous observations, it is likely that the observed epimerisation occurs through base-mediated enolisation at the β -lactone C(3)-position, then reprotonation.^{25–28}

Scope and limitations

With optimised conditions in hand, the generality of this methodology was investigated through variation of the aryl acetic acid component (Fig. 5). Electron-donating groups in the aryl C(4)-position were well tolerated, giving β -lactones **48** and **49** in good yields, with high diastereo- and enantioselectivity (70–74%, 91 : 9–>95 : 5 dr, both 95 : 5 er). Halogens were also well-tolerated in this position (61–84%, 94 : 6–95 : 5 er), although β -lactones **50** and **51** were isolated with reduced diastereoselectivity (82 : 18–84 : 16 dr), which may be due to the increased susceptibility towards epimerisation at this stereocentre under the reaction conditions. Further variation around the aryl ring was also successful, with 3-OMe, 3,5-OMe and even 3-CF₃ β -lactones **52–54** formed in synthetically useful yields, with good diastereo- and enantioselectivities (41–73%, 86 : 14–89 : 11 dr, 90 : 10–95 : 5 er). Pleasingly, heteroaryl substituents were also well-tolerated, with β -lactones **55–57** prepared in good to high yields with high diastereo- and enantioselectivity (69–90%, 86 : 14–89 : 11 dr, 90 : 10–98 : 2 er). Single crystal X-ray analysis of **55** confirmed the relative and absolute configuration, which aligns with that within the C(3)-alkyl scope. Subsequent investigations focused on the scope of the α -ketophosphonate. Incorporation of the electron-withdrawing 4-F₃CC₆H₄ substituents gave a disappointing 48% yield of β -lactone **58**, although good diastereoselectivity and excellent enantioselectivity were observed (89 : 11 dr, 99 : 1 er). Pleasingly, the reaction of both 4-tolylacetic acid and 3-thiophenylacetic acid with 4-ClC₆H₄- and 4-FC₆H₅-substituted

Table 2 Variation of reaction conditions^a

Entry	Variation	Yield ^d /%	dr ^e	er ^f
1	None	39	90 : 10	98 : 2
2	2 equiv. of <i>i</i> -Pr ₂ NEt in (i)	55	93 : 7	99 : 1
3 ^b	3 equiv. 47 , added over 1 min	72	87 : 13	96 : 4
4 ^{b,c}	3 equiv. 47 , added over 5 min	74	90 : 10	96 : 4
5 ^{b,c}	3 equiv. 47 , added over 15 min	56	88 : 12	96 : 4
6	(2 <i>S</i> ,3 <i>R</i>)-HyperBTM (2.5 mol%)	38	82 : 18	83 : 17

^a *t*-BuCOCl (0.6 mmol), *i*-Pr₂NEt (0.6 mmol) and acid **47** (0.4 mmol) in MTBE (2 mL, 0.1 M) was stirred at 0 °C for 10 min, then *i*-Pr₂NEt (0.2 mmol), α -ketophosphonate **4** (0.2 mmol) and (2*S*,3*R*)-HyperBTM **1** (5 mol%) at 25 °C for 16 h. ^b 1.6 mL MTBE used in (i), then 0.4 mL added in (ii) to ensure all components rinsed into flask. ^c Rate of addition controlled using syringe pump, 0.32 mL min⁻¹ for 5 min or 0.11 mL min⁻¹ for 15 min. ^d Isolated yield. ^e Determined by ¹H NMR of crude reaction mixture. ^f Determined by HPLC analysis on a chiral stationary phase.



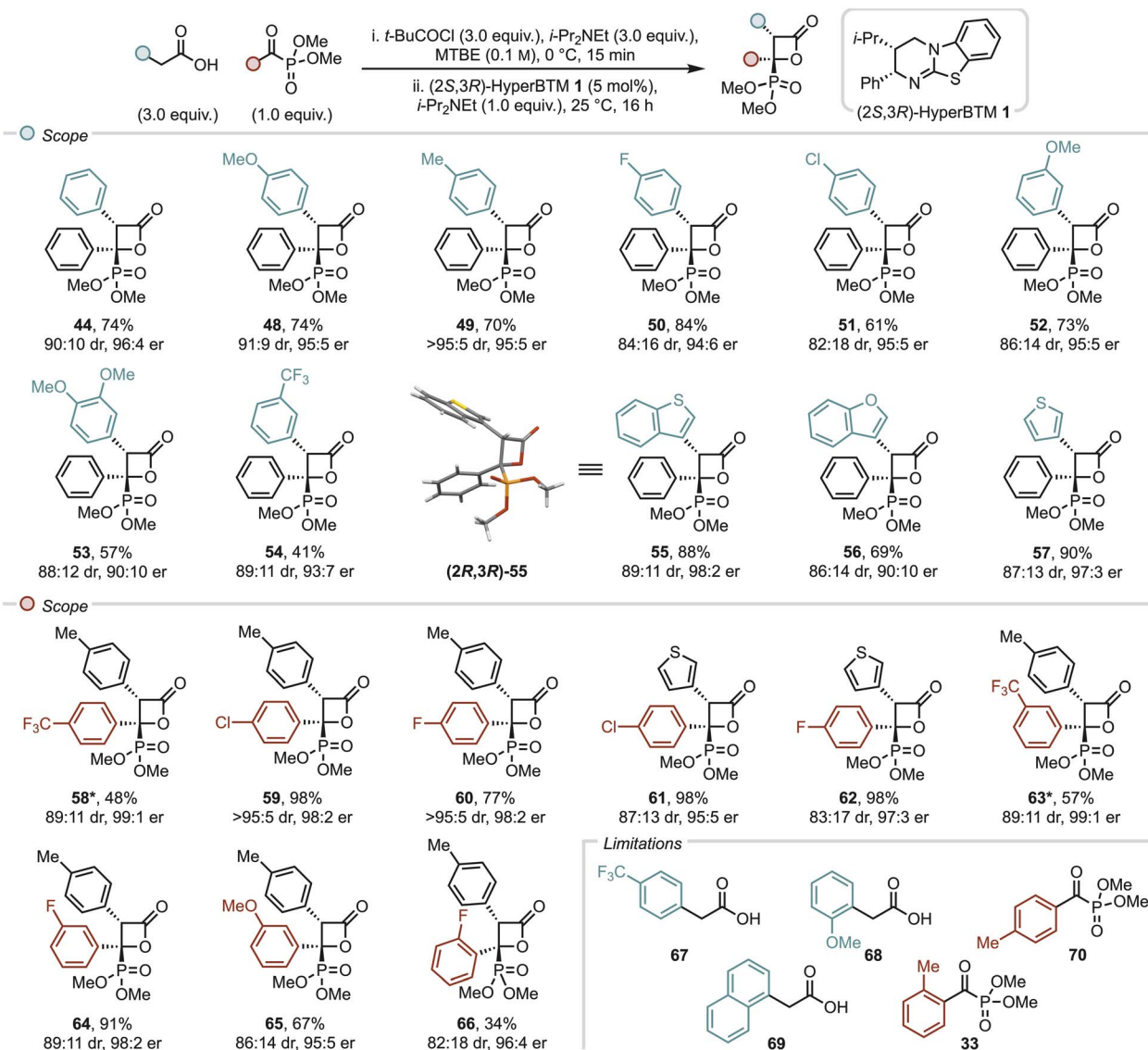


Fig. 5 Scope and limitations of formal [2 + 2] cycloaddition of (hetero)arylacetic acids with α -ketophosphonates. All yields are isolated yields, dr determined by ¹H NMR of crude reaction mixture, er determined by HPLC analysis on a chiral stationary phase. * α -ketophosphonate starting material showed dimerization over time (see ESI†).

benzoylphosphonates worked well, giving β -lactones **59–62** in high yields, with high diastereoselectivity and excellent enantioselectivity (77–98%, 83 : 17–>95 : 5 dr, 95 : 5–98 : 2 er).

Electron-withdrawing groups in other positions were also well-tolerated in this methodology with β -lactones **63–65** prepared in good yields with good diastereoselectivity and excellent enantioselectivity throughout (57–91%, 86 : 14–89 : 11 dr, 95 : 5–99 : 1 er). Interestingly, although aryl C(2)-substituents had not been tolerated in the α -ketophosphonate scope in the reaction with α -silyl acids (Fig. 2) or in the arylacetic acid scope (Fig. 5), 2-FC₆H₅ β -lactone **66** was prepared in a synthetically useful 34% yield, with modest diastereoselectivity (82 : 18 dr) but excellent enantioselectivity (96 : 4 er). Unfortunately, strongly Hammett electron-withdrawing 4-F₃CC₆H₄-phenylacetic acid **67** showed low reactivity under the reaction conditions, which may be due to reduced nucleophilicity of the

intermediate C(1)-ammonium enolate species. Sterically hindered acids **68** and **69** were also not tolerated. Disappointingly, the incorporation of an electron-donating methyl group in either the 4- or 2-position of the aryl-substituent of the phosphonate (**70** and **32**) showed no conversion to the desired β -lactone products, which presumably reflects the reduced electrophilicity of the carbonyl carbon, and/or steric hindrance in the case of the 2-MeC₆H₅ substituent.

Proposed mechanism

Based upon these observations and following established precedent, a catalytic cycle for the enantioselective formal [2 + 2] cycloaddition of C(1)-ammonium enolates and α -ketophosphonates is presented (Fig. 6a) with the method of C(1)-ammonium enolate generation dependent upon the starting material. When (hetero)arylacetic mixed anhydrides **71** are used



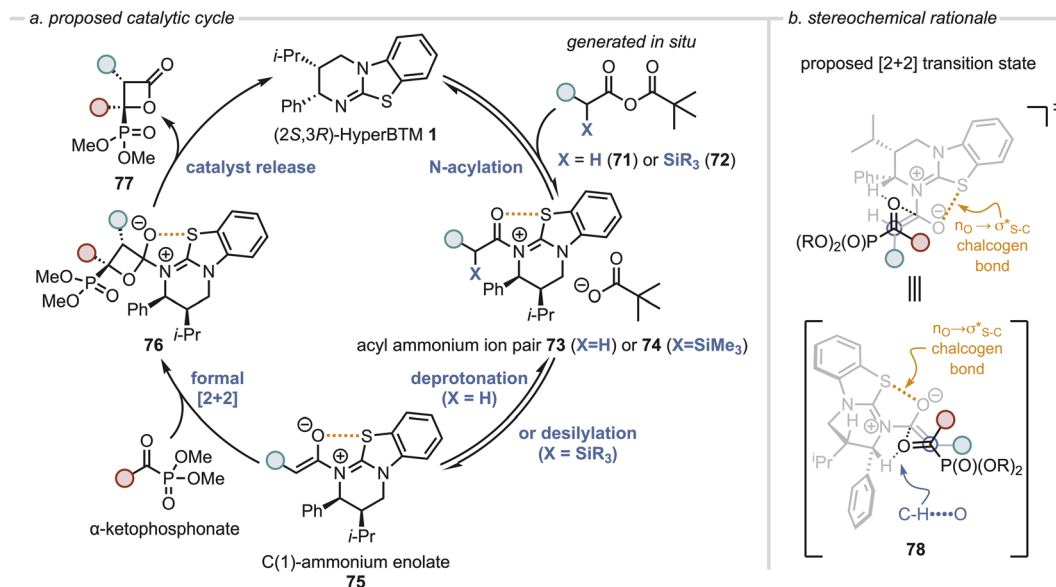


Fig. 6 Proposed mechanism and stereochemical rationale.

(X = H), *N*-acylation of (2*S*,3*R*)-HyperBTM **1** occurs reversibly to generate acyl ammonium ion pair **73**, with deprotonation at the α -position generating the corresponding (*Z*)-C(1)-ammonium enolate **75**. When an excess of (\pm)- α -alkyl- α -silyl mixed anhydride **72** is used, following our previous work preferential acylation of the (*R*)-enantiomer of **72** in a kinetic resolution process is assumed to lead to acyl ammonium ion pair **74** and enantioenriched anhydride **72**. Desilylation to generate the corresponding C(1)-ammonium enolate **75** occurs, which may be promoted by the pivalate counterion or an alternative nucleophile such as a chloride anion, or through a Brook-type *C*- to *O*-silyl rearrangement followed by *O*-desilylation.²¹ In both cases, key to the observed stereochemical outcome is formation of the (*Z*)-ammonium enolate and a stabilizing 1,5- $O\cdots S$ chalcogen bonding interaction ($n_O \rightarrow \pi^*_{S-C}$) which ensures coplanarity between the 1,5- O and S -atoms and provides a conformational bias.^{29–30} The relative and absolute configuration observed within the major diastereoisomer of the β -lactone products is consistent with that previously observed in related formal [2 + 2] cycloadditions of C(1)-ammonium enolates with trifluoromethylketones,²³ isatins⁵¹ and pyrazolones⁵² and so by analogy a similar concerted asynchronous formal [2 + 2] cycloaddition pathway *via* transition state assembly **78** to give **77** is proposed. Following precedent,^{21,51–53} we speculate that this transition state assembly can be stabilised a non-classical $CH\cdots O$ interaction between the acidic α -C-H of the substrate-bound catalyst and the carbonyl $C=O$ (Fig. 6b).⁵⁴ Subsequent catalyst release *via* collapse of the spirocyclic tetrahedral intermediate **76** generates the β -lactone **77** in high diastereo- and enantioselectivity.

Conclusion

This manuscript reports the development of a highly diastereo- and enantioselective formal [2 + 2] cycloaddition of α -

unsubstituted, α -alkyl and α -(hetero)aryl-substituted C(1)-ammonium enolates with α -ketophosphonates using the isothiurea catalyst (2*S*,3*R*)-HyperBTM **1**. The scope and limitations of this process have been explored, with good yields and high stereoselectivity observed across a broad range of substrate derivatives incorporating varied substitution at the C(3)- and C(4)-positions as well as the phosphonate group. This cycloaddition procedure is also amenable to scale up using bench grade solvents and reagents, with effective conversion on a 1 g scale demonstrated. The further application of this methodology towards unsymmetrical phosphonates is currently underway within our laboratory.

Data availability

All data (experimental procedures and characterization data) that support the findings of this study are available within the article and its ESI.† Crystallographic data for compounds (2*R*,3*R*)-**18**, (2*R*,3*R*)-**26** and (2*R*,3*R*)-**55** have been deposited with the Cambridge Crystallographic Data Centre under deposition numbers 2395570, 2395571 and 2395572, respectively. The research data supporting this publication can be accessed at: DOI: <https://doi.org/10.17630/a6b1715c-641b-47c2-8a28-d493726f8e5f>, 2024, data underpinning: “Isothiurea-Catalysed Enantioselective Synthesis of Phosphonate-Functionalised β -lactones”, University of St Andrews Research Portal.

Author contributions

ADS conceived the project. FMP and YW carried out all experimental studies in consultation with HP and ADS. FMP, YW and ADS wrote the manuscript. DBC, APM and AMZS carried out single crystal X-ray analysis. All authors agreed on the finalised



version of the manuscript. FMP and YW contributed equally to this paper and both have the right to put their name first.

Conflicts of interest

The authors declare no competing interests.

Acknowledgements

The research leading to these results has received funding from AstraZeneca (FMP), the EaSI-CAT Centre for Doctoral Training (FMP), the CSC-St Andrews PhD Scholarship Scheme (YW) and the EPSRC (CMY, EP/S019359/1). ADS thanks the EPSRC Programme Grant “Boron: Beyond the Reagent” (EP/W007517) for support. The authors thank Dr Tengfei Kang (St Andrews) for valuable discussions and suggestions. To meet institutional and research funder open access requirements, any accepted manuscript arising shall be open access under a Creative Commons Attribution (CC BY) reuse licence with zero embargo.

Notes and references

- J. B. Rodriguez and C. Gallo-Rodriguez, *ChemMedChem*, 2019, **14**, 190–216.
- G. M. Dill, R. D. Sammons, P. C. C. Feng, F. Kohn, K. Kretzmer, A. Mehrsheikh, M. Bleeke, J. L. Honegger, D. Farmer, D. Wright and E. A. Hauptfear, in *Glyphosate Resistance in Crops and Weeds*, ed. V. K. Nandula, Wiley, 1st edn, 2010, pp. 1–33.
- N. Popovics-Tóth and E. Bálint, *Acta Chim. Slov.*, 2022, **69**, 735–755.
- D. Lanzinger, S. Salzinger, B. S. Soller and B. Rieger, *Ind. Eng. Chem. Res.*, 2015, **54**, 1703–1712.
- S. Samanta and C.-G. Zhao, *J. Am. Chem. Soc.*, 2006, **128**, 7442–7443.
- T. Mandal, S. Samanta and C.-G. Zhao, *Org. Lett.*, 2007, **9**, 943–945.
- X. Chen, J. Wang, Y. Zhu, D. Shang, B. Gao, X. Liu, X. Feng, Z. Su and C. Hu, *Chem.–Eur. J.*, 2008, **14**, 10896–10899.
- S. Kayal and S. Mukherjee, *Org. Lett.*, 2015, **17**, 5508–5511.
- J. Yu, X. Zhao, Z. Miao and R. Chen, *Org. Biomol. Chem.*, 2011, **9**, 6721.
- V. B. Gondi, K. Hagihara and V. H. Rawal, *Angew. Chem., Int. Ed.*, 2009, **48**, 776–779.
- M. Frings, I. Thomé, I. Schiffrers, F. Pan and C. Bolm, *Chem.–Eur. J.*, 2014, **20**, 1691–1700.
- S. L. Robinson, J. K. Christenson and L. P. Wackett, *Nat. Prod. Rep.*, 2019, **36**, 458–475.
- H. W. Yang and D. Romo, *Tetrahedron*, 1999, **55**, 6403–6434.
- A. D. Smith, J. Douglas, L. C. Morrill and E. Richmond, in *Methods and Applications of Cycloaddition Reactions in Organic Syntheses*, John Wiley & Sons, Ltd, 2014, pp. 89–114.
- K. N. Van, L. C. Morrill, A. D. Smith and D. Romo, in *Lewis Base Catalysis in Organic Synthesis*, John Wiley & Sons, Ltd, 2016, pp. 527–654.
- S. Mukherjee and A. T. Biju, *Chem.–Asian J.*, 2018, **13**, 2333–2349.
- L. C. Morrill and A. D. Smith, *Chem. Soc. Rev.*, 2014, **43**, 6214–6226.
- C. McLaughlin, A. M. Z. Slawin and A. D. Smith, *Angew. Chem., Int. Ed.*, 2019, **58**, 15111–15119.
- K. J. Schwarz, J. L. Amos, J. C. Klein, D. T. Do and T. N. Snaddon, *J. Am. Chem. Soc.*, 2016, **138**, 5214–5217.
- S. Y. Lee, S. Neufeind and G. C. Fu, *J. Am. Chem. Soc.*, 2014, **136**, 8899–8902.
- Y. Wang, C. M. Young, H. Liu, W. C. Hartley, M. Wienhold, D. B. Cordes, A. M. Z. Slawin and A. D. Smith, *Angew. Chem., Int. Ed.*, 2022, **61**, e202208800.
- J. Sun, F. He, Z. Wang, D. Pan, P. Zheng, C. Mou, Z. Jin and Y. R. Chi, *Chem. Commun.*, 2018, **54**, 6040–6043.
- D.-J. Barrios Antúnez, M. D. Greenhalgh, A. C. Brueckner, D. M. Walden, P. Elías-Rodríguez, P. Roberts, B. G. Young, T. H. West, A. M. Z. Slawin, P. Ha-Yeon Cheong and A. D. Smith, *Chem. Sci.*, 2019, **10**, 6162–6173.
- D. S. Noyce and E. H. Banitt, *J. Org. Chem.*, 1966, **31**, 4043–4047.
- A. Matviitsuk, M. D. Greenhalgh, J. E. Taylor, X. B. Nguyen, D. B. Cordes, A. M. Z. Slawin, D. W. Lupton and A. D. Smith, *Org. Lett.*, 2020, **22**, 335–339.
- G. Kang, M. Yamagami, S. Vellalath and D. Romo, *Angew. Chem., Int. Ed.*, 2018, **57**, 6527–6531.
- S. R. Smith, J. Douglas, H. Prevet, P. Shapland, A. M. Z. Slawin and A. D. Smith, *J. Org. Chem.*, 2014, **79**, 1626–1639.
- D.-S. Ji, H. Liang, K.-X. Yang, Z.-T. Feng, Y.-C. Luo, G.-Q. Xu, Y. Gu and P.-F. Xu, *Chem. Sci.*, 2022, **13**, 1801–1807.
- V. B. Birman, X. Li and Z. Han, *Org. Lett.*, 2007, **9**, 37–40.
- P. Liu, X. Yang, V. B. Birman and K. N. Houk, *Org. Lett.*, 2012, **14**, 3288–3291.
- M. E. Abbasov, B. M. Hudson, D. J. Tantillo and D. Romo, *J. Am. Chem. Soc.*, 2014, **136**, 4492–4495.
- E. R. T. Robinson, D. M. Walden, C. Fallan, M. D. Greenhalgh, P. H.-Y. Cheong and A. D. Smith, *Chem. Sci.*, 2016, **7**, 6919–6927.
- 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. Cheong and A. D. Smith, *Angew. Chem., Int. Ed.*, 2018, **57**, 3200–3206.
- C. M. Young, A. Elmi, D. J. Pascoe, R. K. Morris, C. McLaughlin, A. M. Woods, A. B. Frost, A. de la Houpliere, K. B. Ling, T. K. Smith, A. M. Z. Slawin, P. H. Willoughby, S. L. Cockroft and A. D. Smith, *Angew. Chem., Int. Ed.*, 2020, **59**, 3705–3710.
- Y. Nagao, S. Miyamoto, M. Miyamoto, H. Takeshige, K. Hayashi, S. Sano, M. Shiro, K. Yamaguchi and Y. Sei, *J. Am. Chem. Soc.*, 2006, **128**, 9722–9729.
- B. R. Beno, K.-S. Yeung, M. D. Bartberger, L. D. Pennington and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 4383–4438.
- D. J. Pascoe, K. B. Ling and S. L. Cockroft, *J. Am. Chem. Soc.*, 2017, **139**, 15160–15167.
- M. Breugst and J. J. Koenig, *Eur. J. Org. Chem.*, 2020, **2020**, 5473–5487.



- 39 A. J. Mukherjee, S. S. Zade, H. B. Singh and R. B. Sunoj, *Chem. Rev.*, 2010, **110**, 4357–4416.
- 40 K. Fujita, M. Iwaoka and S. Tomoda, *Chem. Lett.*, 1994, **23**, 923–926.
- 41 K. Fujita, K. Murata, M. Iwaoka and S. Tomoda, *J. Chem. Soc., Chem. Commun.*, 1995, 1641.
- 42 K. Fujita, K. Murata, M. Iwaoka and S. Tomoda, *Tetrahedron Lett.*, 1995, **36**, 5219–5222.
- 43 T. Wirth, *Angew. Chem., Int. Ed.*, 1995, **34**, 1726–1728.
- 44 C. Bleiholder, R. Gleiter, D. B. Werz and H. Köppel, *Inorg. Chem.*, 2007, **46**, 2249–2260.
- 45 S. Kolb, G. A. Oliver and D. B. Werz, *Angew. Chem., Int. Ed.*, 2020, **59**, 22306–22310.
- 46 S. Benz, J. López-Andarias, J. Mareda, N. Sakai and S. Matile, *Angew. Chem., Int. Ed.*, 2017, **56**, 812–815.
- 47 P. Wonner, L. Vogel, M. Düser, L. Gomes, F. Kniep, B. Mallick, D. B. Werz and S. M. Huber, *Angew. Chem., Int. Ed.*, 2017, **56**, 12009–12012.
- 48 W. Wang, H. Zhu, S. Liu, Z. Zhao, L. Zhang, J. Hao and Y. Wang, *J. Am. Chem. Soc.*, 2019, **141**, 9175–9179.
- 49 J. Merad, J. Pons, O. Chuzel and C. Bressy, *Eur. J. Org. Chem.*, 2016, **2016**, 5589–5610.
- 50 V. B. Birman, *Aldrichimica Acta*, 2016, **49**, 23–33.
- 51 Y. Abdelhamid, K. Kasten, J. Dunne, W. C. Hartley, C. M. Young, D. B. Cordes, A. M. Z. Slawin, S. Ng and A. D. Smith, *Org. Lett.*, 2022, **24**, 5444–5449.
- 52 A. Conboy, A. S. Goodfellow, K. Kasten, J. Dunne, D. B. Cordes, M. Bühl and A. D. Smith, *Chem. Sci.*, 2024, **15**, 8896–8904.
- 53 J. Wu, C. M. Young, A. A. Watts, A. M. Z. Slawin, G. R. Boyce, M. Bühl and A. D. Smith, *Org. Lett.*, 2022, **24**, 4040–4045.
- 54 S. K. Agrawal, P. K. Majhi, A. S. Goodfellow, R. K. Tak, D. B. Cordes, A. P. McKay, K. Kasten, M. Bühl and A. D. Smith, *Angew. Chem., Int. Ed.*, 2024, **63**, e202402909.

