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Probing Regio- and Enantioselectivity in the Formal [2 + 2] Cycloaddition of C(1)-Alkyl Ammonium Enolates with β- and α,β-Substituted Trifluoromethylenones

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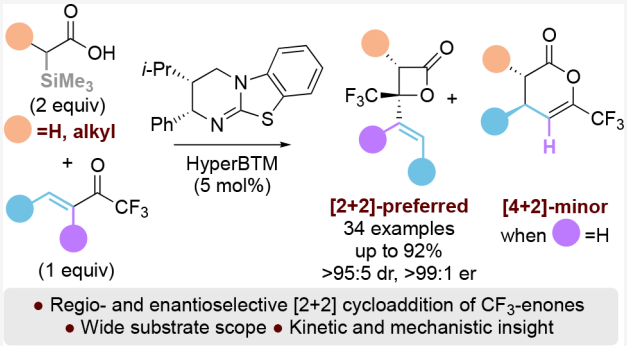
ABSTRACT: The isothiourea-catalyzed regio- and enantioselective formal [2 + 2] cycloaddition of C(1)-alkyl and C(1)-unsubstituted ammonium enolates with β- and α,β-substituted trifluoromethylenones has been developed. In all cases, preferential [2 + 2]-cycloaddition over the alternative [4 + 2]-cycloaddition is observed, giving β-lactones with excellent diastereo- and enantioselectivity (34 examples, up to >95:5 dr, >99:1 er). The regioselectivity of the process was dictated by the nature of the substituents on both reaction components. Solely [2 + 2] cycloaddition products are observed when using α,β-substituted trifluoromethylenones or α-trialkylsilyl acetic acid derivatives; both [2 + 2] and [4 + 2] cycloaddition products are observed when using β-substituted trifluoromethylenones and α-alkyl-α-trialkylsilyl acetic acids as reactants, with the [2 + 2] cycloaddition as the major reaction product. The beneficial role of the α-silyl substituent within the acid component in this protocol has been demonstrated by control experiments.



■ INTRODUCTION

The asymmetric synthesis of β-lactones has attracted considerable interest in organic chemistry due to their versatility as synthetic intermediates as well as their prevalence in a wide range of biologically active molecules.[1] Enantioenriched β-lactones can be accessed in a number of ways, with Lewis acid- or Lewis base-catalyzed formal cycloadditions being the most common.[2,3] Lewis base-catalyzed approaches typically proceed through the formal [2 + 2] cycloaddition of ammonium enolates with ketenes, aldehydes, or highly reactive ketones.[4−8] In related Lewis base-catalyzed processes, trifluoromethylenones have been extensively explored as electrophiles in formal [4 + 2] cycloadditions such as the isothiourea-catalyzed reaction of trifluoromethylenones with arylacetic acid derivatives (Scheme 1a).[9,10] In this case, exclusive formation of [4 + 2]-products was observed, giving C(6)-trifluoromethyldihydropyranones in high yields and excellent enantioselectivity. However, use of 2-(pyrrol-1-yl)acetic acid in this protocol notably gave a 50:50 ratio of products arising from formal [4 + 2] and [2 + 2] cycloaddition reactions (Scheme 1b),[11] indicating that regioselective reaction directly with the carbonyl of the α,β-unsaturated system to generate the corresponding β-lactone is feasible and is dependent upon the C(1)-substitution of the ammonium enolate. Intrigued by this observation, in this manuscript we report the regio- and enantioselective addition of a range of C(1)-alkyl substituted or unsubstituted ammonium enolates, prepared through a recently reported desilylation process,[12] to trifluoromethylenones.

Systematic variation of the substituents within both the trifluoromethylenone and the C(1)-alkyl substituted or unsubstituted ammonium enolate provide preferential, and in some cases exclusive, access to highly functionalized β-lactones with high enantioselectivity.

■ RESULTS AND DISCUSSION

Investigation of Optimal Reaction Conditions. An initial trial was performed using α-trimethylsilyl acetic acid **1** as a C(1)-ammonium enolate precursor with β-phenyl trifluoromethylenone **2** (Table 1). Treatment of acid **1** with pivaloyl chloride (3 equiv) in MTBE to generate the corresponding mixed anhydride, followed by addition of (2*S*,3*R*)-HyperBTM **4** (5 mol %) and enone **2** at room temperature, gave exclusively the formal [2 + 2]-cycloaddition product, β-lactone **3**, in high yield (75%) and excellent enantioselectivity (92:8 er). Attempted optimization varied a range of reaction

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Scheme 1. Isothiourea-Catalyzed Enantioselective Cycloadditions with Trifluoromethylenones

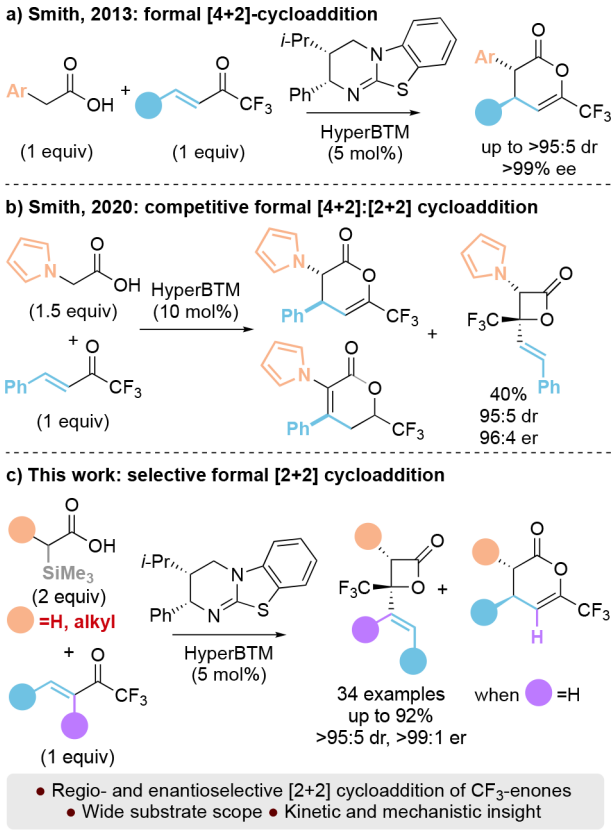
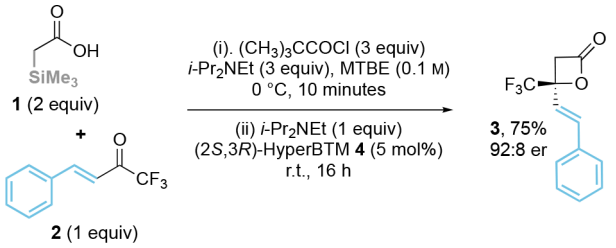
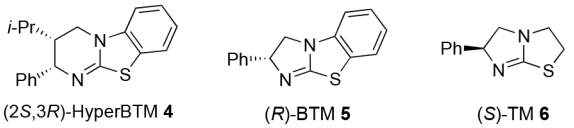


Table 1. Optimization of Reaction Conditions[a]



Isothioureas:



entry	variant	yield[b] (%)	er[c]
1	none	75	92:8
2	(*R*)-BTM **5** as catalyst	12	75:25
3	(*S*)-TM **6** as catalyst	0	–
4	Et_3N as base	45	92:8
5	$NaHCO_3$ as base	30	–
6	Cs_2CO_3 as base	30	–
7	PhC(O)Cl	57	89:11
8	4-$NO_2C_6H_4C(O)Cl$	48	89:11
9	**1** (1 equiv)	56[d]	–
10	0 °C for (ii)	80	89:11

[a]$(CH_3)_3CC(O)Cl$ (1.2 mmol), *i*-Pr_2NEt (1.2 mmol) and acid **1** (0.8 mmol) in MTBE (4 mL, 0.1 M) was stirred at 0 °C for 10 min before addition of *i*-Pr_2NEt (0.4 mmol), enone **2** (0.4 mmol), and (2*S*,3*R*)-HyperBTM **4** (5 mol %) at r.t. for 16 h. MTBE = methyl *tert*-butyl ether. r.t. = room temperature (18 °C). BTM = benzotetramisole. TM = tetramisole. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Determined by ^1H NMR analysis of the crude reaction mixture.

parameters, including solvent, catalyst, temperature, auxiliary base, and acid chloride. A range of polar and nonpolar solvents were tested, but in all cases led to reduced yield and enantioselectivity compared with MTBE (see SI). Using (*R*)-BTM **5** gave significantly reduced conversion to the product, giving 12% isolated yield of **3** in 75:25 er (entry 2), while (*S*)-tetramisole **6** gave no conversion to the product (entry 3). Further variation of base showed that using triethylamine instead of *N*,*N*-diisopropylethylamine did not affect the enantioselectivity, but gave significantly decreased yield (entry 4), while inorganic bases Cs_2CO_3 and $NaHCO_3$ led to poor reactivity (entries 5−6). Using benzoyl chloride and *para*-nitrobenzoyl chloride to generate the corresponding mixed anhydride resulted in reduced product yields and enantioselectivity (entries 7−8). The use of 1 equiv of acid **1** led to reduced product conversion (entry 9) while reducing the temperature to 0 °C gave the product with slightly reduced er (entry 10).

Scope, Limitations, and Derivatizations. With the optimal conditions in hand, the substrate scope of this process was explored, initially using **1** as the ammonium enolate precursor, with the effect of variation in product distribution between [2 + 2]- and [4 + 2]-cycloaddition considered (Table 2). In all cases, *β*-substituted trifluoromethylenones gave exclusive [2 + 2]-cycloaddition, giving C(3)-unsubstituted *β*-lactones **7**−**13**. Products **7**−**9**, bearing a *para*-Br, *ortho*-Br, and *meta*-OMe substituents on the *β*-aryl group, respectively, were obtained in good yields (65% to 78%) and enantioselectivities (89:11 er to 92:8 er). *α*,*β*-Disubstituted trifluoromethylenones gave access to *β*-lactones **10**−**13** with overall good yield (52% to 92%) and high levels of enantioselectivity (92:8 to 94:6 er). However, no reactivity was observed when employing *α*-benzyl-*β*-phenyl substituted trifluoromethylenone **14a** or *β*-Me substituted enone **14b** as the electrophile with only unreacted enones returned (Table 2).

Further substrate exploration extended this protocol to the variation of *α*-silyl-*α*-alkyl substituted acids and *β*-substituted trifluoromethylenones (Table 3A). Interestingly, the incorporation of an *α*-alkyl substituent into the *α*-silyl acid component led to the formation of 5−20% of the [4 + 2]-cycloaddition product in this series, although the [2 + 2]-cycloaddition was still favored. For example, using *α*-methyl-*α*-trimethylsilyl substituted acid as the anhydride precursor and *β*-phenyl-trifluoromethylenone as reactant gave **15** in 75% yield (85:15 dr) in excellent enantioselectivity (99:1 er), and 85:15 ratio of ([2 + 2]:[4 + 2] products). Variation of the *β*-substituent within the enone through the incorporation of *para*-Br, *para*-Cl, *para*-F, and *para*-CF_3 substituents gave **16**−**19** with excellent diastereo- and enantioselectivity (up to 90:10 dr, >99:1 er) in good yield (59% to 76%), and with preferential [2 + 2]-cycloaddition ([2 + 2]:[4 + 2] = 85:15 to >95:5). The absolute configurations of products **17** and **18** were confirmed by X-ray crystallographic analysis, with all other products assigned by analogy. *meta*-Substitution within the enone gave *β*-lactones **20**−**22** in diminished but acceptable yields (51% to 64%), with good diastereoselectivity and exceptional enantio-control (85:15 dr, up to >99:1 er), and preferential [2 + 2]-regioselectivity ([2 + 2]:[4 + 2] = 82:18 to 94:6).

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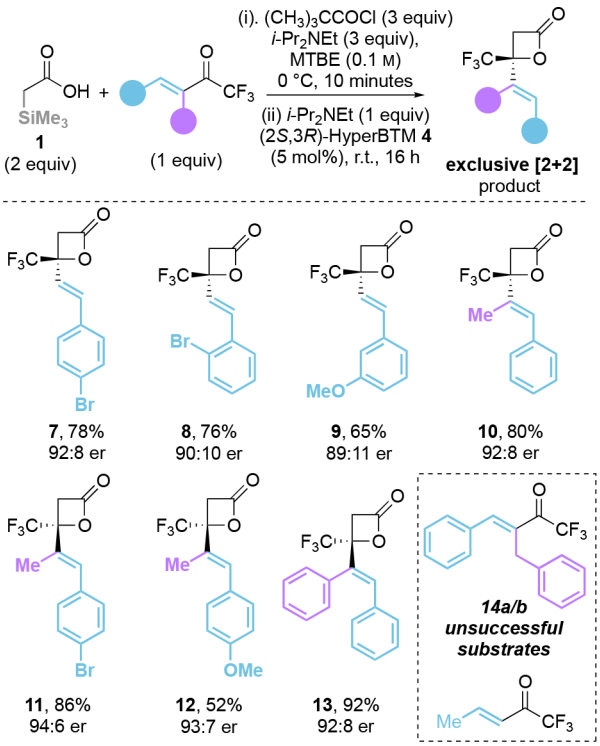
Table 2. Scope and Limitations: α-Trimethylsilyl Acid 1 and Trifluoromethylenone Variation[a]



[a] $(CH_3)_3CC(O)Cl$ (1.2 mmol), i-Pr_2NEt (1.2 mmol), and acid **1** (0.8 mmol) in MTBE (4 mL, 0.1 M) was stirred at 0 °C for 10 min before addition of i-Pr_2NEt (0.4 mmol), enone **2** (0.4 mmol), and (2*S*,3*R*)-HyperBTM **4** (5 mol %) at r.t. for 16 h. All reported isolated yields all product er's determined by HPLC analysis on a chiral stationary phase.

Incorporation of a β-1- or 2-naphthyl substituent within the trifluoromethylenone gave products **23** and **24** in moderate yield (54% and 64%) but excellent diastereo- and enantioselectivity (both 90:10 dr, >99:1 er), with 1-naphthyl substituted [2 + 2]-product **24** obtained exclusively. The use of trifluoromethylenones bearing *ortho*-substituted-β-aryl substituents also led to improved selectivity for [2 + 2] over [4 + 2] products, giving β-lactones **25** and **26** in 60% and 46% yield and >99:1 er, with ([2 + 2]:[4 + 2] = 90:10 and >95:5 respectively). Variation of the alkyl substituent within the α-silyl acid was next explored with β-phenyl trifluoromethylenone **2** used as a standard electrophile. Ethyl, allyl, alkynyl, benzyl, and 2-naphthylmethyl substituted acid derivatives demonstrated good reactivity. The desired [2 + 2] products **27**−**31** were isolated in 52% to 60% yield, 80:20 to 90:10 dr, up to >99:1 er, and with preferential [2 + 2]-cycloaddition ([2 + 2]:[4 + 2] = 80:20 to 86:14). Further exploration of the substrate scope focused on the reactivity of α-trimethylsilyl-α-methyl substituted acid with a range of α-methyl substituted β-aryl trifluoromethylenones (Table 3B). Notably, the introduction of this substitution pattern led to exclusive [2 + 2] cycloaddition in all cases. Formal [2 + 2] cycloaddition products **32**−**35** were obtained in good yields (up to 80%) with exceptional diastereoselectivity (>95:5 dr) and excellent enantioselectivity (92:8 er to >99:1 er). The absolute configuration of product **34** was confirmed by X-ray crystallographic analysis. Variation of the α-alkyl substituent within the α-trimethylsilyl acid gave products **36**−**40** in good yields (up to 78%), and excellent enantioselectivity (up to >99:1 er for the major enantiomer, 98:2 er for the minor enantiomer), although with moderate diastereoselectivity (67:33 dr to 75:25 dr). In contrast to the unsubstituted α-trimethylsilyl acetic acid **1**, α-alkyl substituted α-trimethylsilyl acids showed no reactivity with α,β-diphenyl substituted trifluoromethylenone **41**. The use of α-isopropyl-α-trimethylsilyl acid **42** also led to returned starting materials with α-methyl-β-phenyl trifluoromethylenone.

Derivatization of β-lactone products **11** and **18** was next investigated to broaden the utility of this methodology (Table 3C). Ring-opening occurs readily with benzylamine as a nucleophile to give the enantioenriched amide product **43** in excellent yield (93%). Alternatively, transformation to an oxetane was achieved through a two-step procedure. Reduction of **11** with DIBAL-H gave diol **44** in 55% yield, followed by ring closure upon treatment with 2,4,6-triisopropylbenzenesulfonyl chloride (TIBS-Cl) to give oxetane product **45** in 84% yield without loss of enantiopurity (96:4 er).

Mechanistic Investigations. To demonstrate the advantage of using α-silyl substituted C(1)-acids as ammonium enolate precursors, control experiments probed the relative reactivity of using acetic acid **46** or acetic anhydride **47** as starting materials. In each case, poor conversion to the corresponding β-lactone **3** was observed, resulting in low isolated product yields although promising er, demonstrating the beneficial reactivity of the silyl-acid starting material (Table 4a). Further experiments compared the reactivity of alternative α-silyl substituents. α-Trimethylsilyl acetic acid and α-trimethylsilyl propionic acid demonstrated excellent reactivity with enone **2** and furnished β-lactones **3** and **15** with exceptional enantioselectivity (92:8 er and 99:1 er respectively). Acids bearing an α-dimethylphenylsilyl group or α-diphenylmethylsilyl group were also tested, giving the corresponding products with competitive enantioselectivity and diastereoselectivity (85:15 to 88:12 dr, 96:4 to >99:1 er) (Table 4b). The product yield decreased with increased steric bulk of the silyl-substituent: for example, both α-dimethylphenylsilyl propionic acid **51** and α-diphenylmethylsilyl propionic acid **52** gave product **15** with similar enantioselectivity (96:4 er and >99:1 er), but in reduced yield (52%). Finally, the use of α-phenyl-α-trimethylsilyl acid **53** was tested, giving exclusively the formal [4 + 2]-cycloaddition product **54** in 52% yield, 87:13 dr, and 99:1 er (Table 4c). Reaction of α-phenyl-α-trimethylsilyl acid **53** with α-methyl-β-phenyl trifluoromethylenone **55** returned only starting materials.

Further mechanistic studies were conducted by using enantiomerically enriched acid (*R*)-**51** with 10 mol % of each enantiomer of HyperBTM **4** separately under standard conditions (Table 5a).[13] Consistent with our previous observations,[12] the relative rates of product formation with enantiomeric catalysts differed significantly, although identical levels of product diastereo- and enantioselectivity were observed throughout these processes. In the mismatched case, treatment of the anhydride generated from (*R*)-**51** with (2*R*,3*S*)-HyperBTM **4** led to relatively slow conversion (35% by ^{19}F NMR after 480 min) to product β-lactone **15** (88:12 dr, 96:4 er, [2 + 2]:[4 + 2] = 85:15). In the matched case, treatment of the anhydride generated from (*R*)-**51** with (2*S*,3*R*)-HyperBTM **4** led to the same stereo- and regioselectivity, but with significantly enhanced conversion (70% by ^{19}F NMR after 480 min) to product β-lactone **15** (88:12 dr, 96:4 er, [2 + 2]:[4 + 2] = 85:15) (Table 5a).

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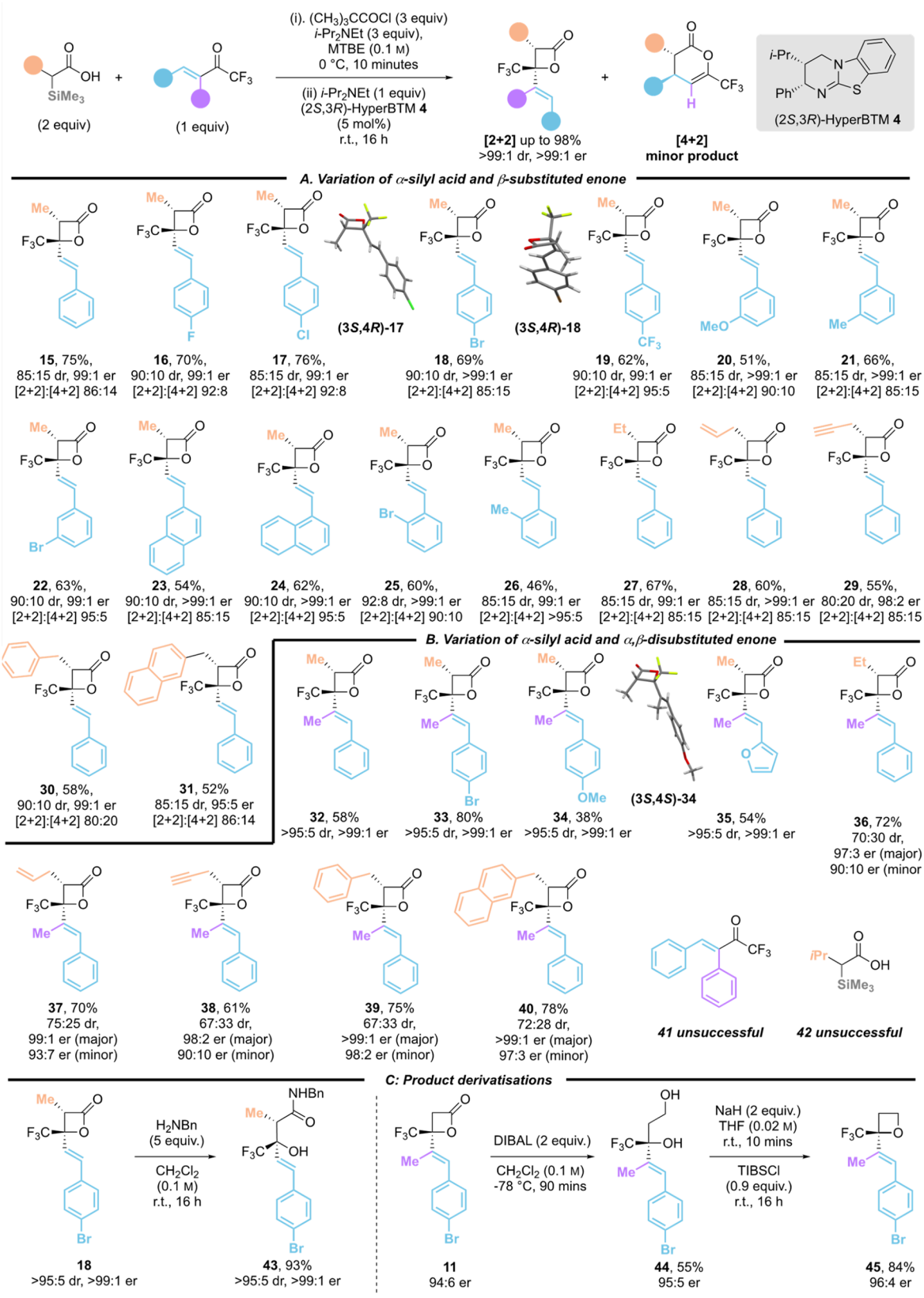
Table 3. Scope and Limitations: Formal [2 + 2] Cycloaddition of α-Trimethylsilyl Acids with Trifluoromethylenones[a,b]



[a]Isolated yields. [b]dr determined by ^{1}H NMR and ^{19}F NMR analysis of the crude reaction product; er determined by HPLC analysis on a chiral stationary phase.

Kinetic analysis using racemic acid **51** and **2** as the electrophile catalyzed by 10 mol % of (2*S*,3*R*)-HyperBTM **4** was monitored using ^{19}F NMR under standard reaction conditions (Table 5b). The rate of formation of product **15** and the rate

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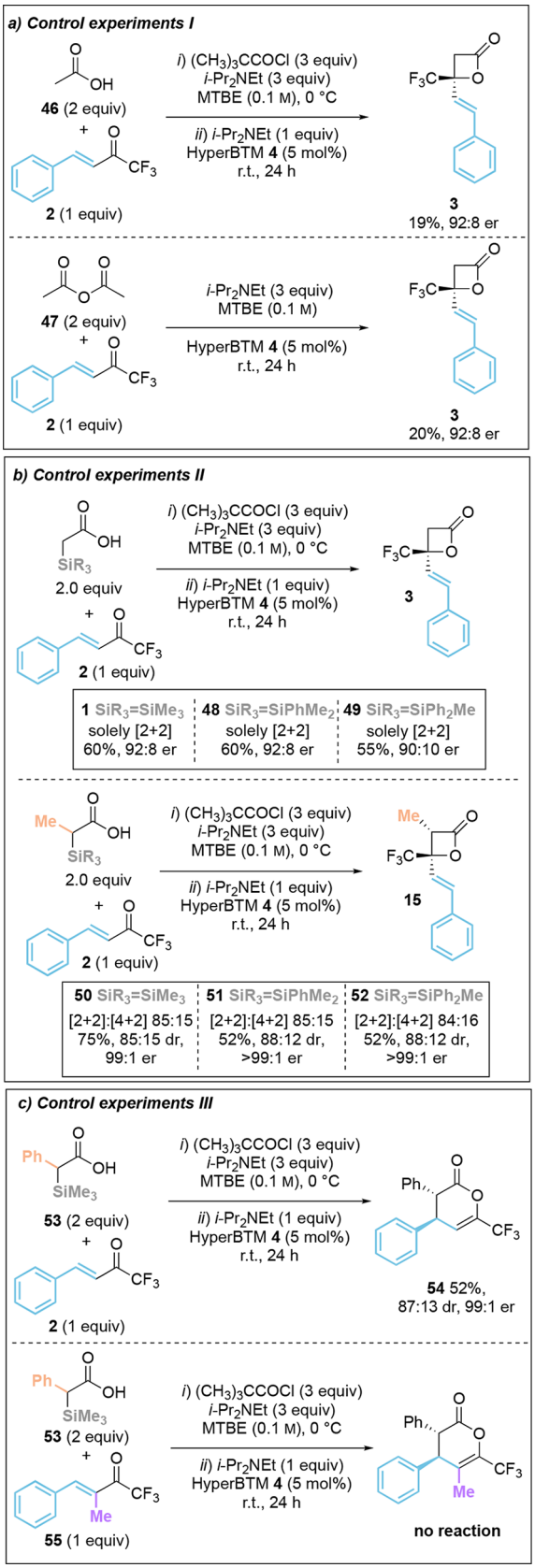
Table 4. Mechanistic Control Experiments[a,b]



[a]Isolated yield. [b]dr determined by ^{1}H NMR and ^{19}F NMR analysis of the crude reaction mixture; er determined by HPLC analysis on a chiral stationary phase.

of consumption of enone **2** both demonstrated linear profiles consistent with a pseudo-zero-order reaction, with identical ratios of β-lactone **15** and [4 + 2] cycloaddition product **56** observed throughout the experiment, consistent with the regioselectivity being kinetically controlled rather than through product interconversion.

Building upon these observations and our previous work, the proposed mechanistic cycle involves initial N-acylation of HyperBTM with the in situ generated mixed anhydride to generate the corresponding acyl ammonium ion pair in a kinetic resolution process.[12] Subsequent desilylation generates the C(1)-ammonium enolate that can undergo either concerted asynchronous [2 + 2] cycloaddition or [4 + 2] cycloaddition with the trifluoromethylenone.[14] The regioselectivity of this process is dictated by steric factors within both reaction components. When α-substituted-β-aryl trifluoromethylenones are used, exclusive [2 + 2] cycloaddition to give the β-lactone products is observed. When α-unsubstituted-β-aryl trifluoromethylenone and α-alkyl-α-silyl acids are used, the C(1)-ammonium enolate can undergo both concerted asynchronous [2 + 2] cycloaddition and [4 + 2] cycloaddition, furnishing β-lactones as the major product accompanied by [4 + 2] cycloaddition as the minor product. Key to the observed stereochemical outcome is a stabilizing 1,5-O···S chalcogen bonding interaction (n_O to σ^*_{S-C}).[15−18] This provides a conformational bias and ensures coplanarity between the 1,5-O- and S-atoms within the (*Z*)-enolate, with preferential addition *anti*- to the stereodirecting phenyl substituent within the catalyst.

■ CONCLUSION

To conclude, a protocol for the diastereo-, enantio-, and regioselective [2 + 2] cycloaddition of β-aryl trifluoromethylenones with α-silyl carboxylic acids catalyzed by the isothiourea HyperBTM under mild and operationally simple conditions has been developed. A broad substrate scope of enantiomerically enriched β-lactone products (34 examples, up to >95:5 dr and >99:1 er) and significantly extended reactivity of C(1)-ammonium enolates has been demonstrated. Control experiments indicate that the α-substituents of the trifluoromethylenone and the α-silyl carboxylic acid play a crucial role in dictating the regioselectivity of this transformation. Solely [2 + 2] cycloaddition was observed when α-silyl acetic acids and α-methyl or α-phenyl substituted β-aryl trifluoromethylenones were used. Both [2 + 2] cycloaddition and Michael addition-lactonization reactions were observed when α-substituted-α-silyl carboxylic acids were used in conjunction with β-aryl trifluoromethylenones lacking a second α-substituent. The bench stable β-lactones are readily derivatized through ring-opening or can be transformed into the corresponding oxetanes without compromising stereochemical integrity.

■ EXPERIMENTAL SECTION

General Information. Reactions involving moisture sensitive reagents were carried out in flame-dried glassware under a nitrogen atmosphere using standard vacuum line techniques and using anhydrous solvents. HyperBTM **4** and benzotetramisole (BTM) **5** were synthesized in house. Tetramisole·HCl **6** was obtained from Sigma-Aldrich. Anhydrous solvents (CH_2Cl_2, PhMe) was obtained after passing through an alumina column (Mbraun SPS-800). Anhydrous MTBE and MeCN was obtained by treatment with activated 4 Å molecular sieves. Petrol is defined as petroleum ether 40−60 °C. All other solvents and commercial reagents were used as supplied without further purification unless otherwise stated. EtOAc,

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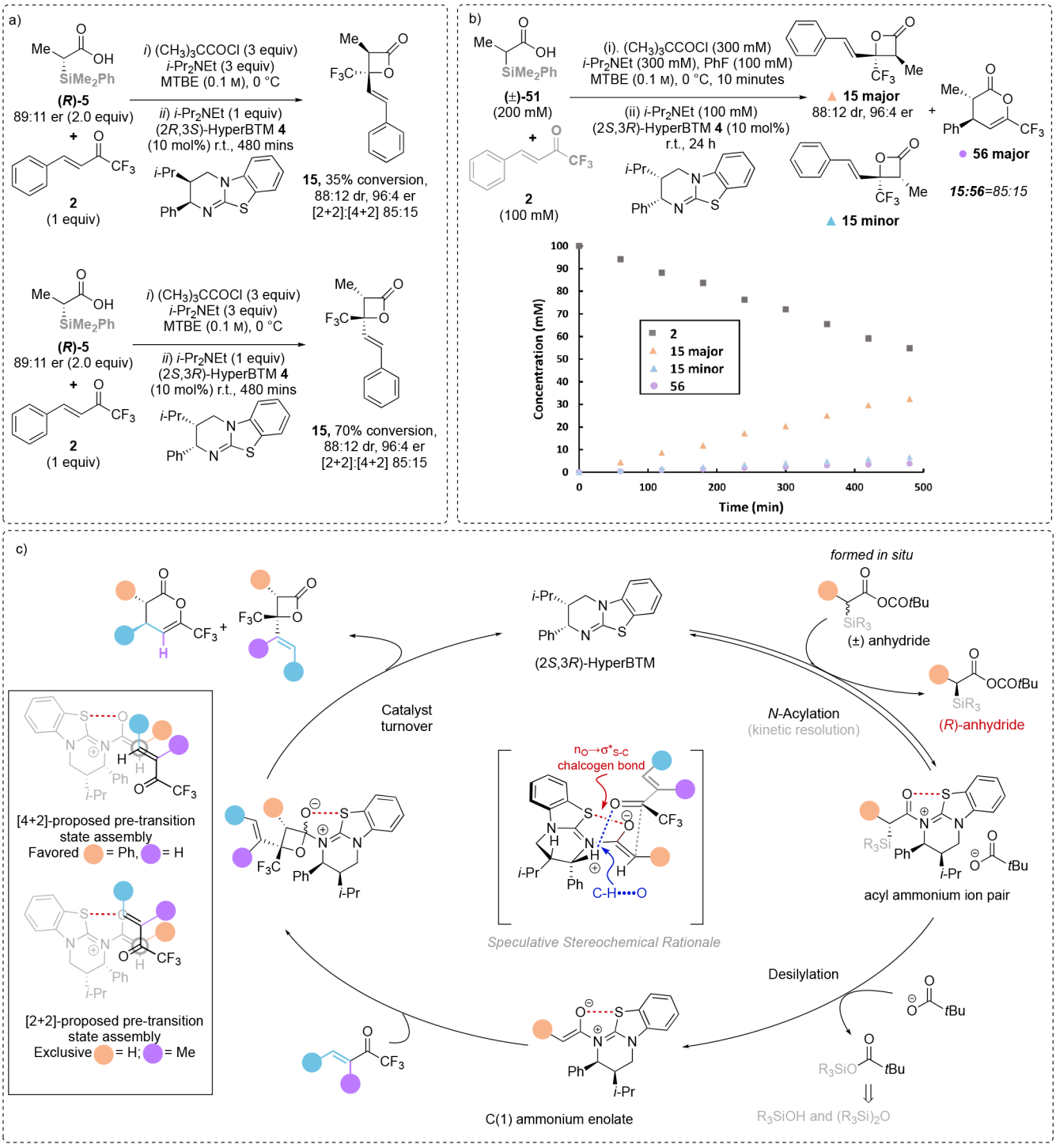
Table 5. (a) Matched and Mismatched Cases; (b) Reaction Profile; (c) Proposed Catalytic Cycle[a,b]



[a]Isolated yield. [b]dr determined by ^{1}H NMR and ^{19}F NMR analysis of the crude reaction mixture; er determined by HPLC analysis on a chiral stationary phase.

Et_2O, CH_2Cl_2, and petrol for purification purposes were used as obtained from suppliers without further purification. Room temperature (r.t.) refers to 20−25 °C. Temperatures of 0 °C and −78 °C were obtained using ice/water and $CO_2(s)$/acetone baths, respectively. Reactions involving heating were performed using a DrySyn block and a contact thermocouple. In vacuo refers to the use either a Büchi Rotavapor R-200 with a Büchi V-491 heating bath and Büchi V-800 vacuum controller; a Büchi Rotavapor R-210 with a Büchi V-491 heating bath and Büchi V-850 vacuum controller; a Heidolph Laborota 4001 with vacuum controller; an IKA RV10 rotary evaporator with an IKA HB10 heating bath and ILMVAC vacuum controller; or an IKA RV10 rotary evaporator with an IKA HB10 heating bath and Vacuubrand CVC3000 vacuum controller. Rotary evaporator condensers are fitted to Julabo FL601 Recirculating Coolers filled with ethylene glycol set to −6 °C. Analytical thin layer chromatography was performed on precoated aluminum plates (Kieselgel 60 F254 silica). TLC visualization was carried out with ultraviolet light (254 nm), followed by staining with a 1% aqueous

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$KMnO_4$ solution. Automated chromatography was performed on a Biotage Isolera Four running Biotage OS578 with a UV−vis detector using the method stated and cartridges filled with Kieselgel 60 silica. Melting points were recorded on an Electrothermal 9100 melting point apparatus and are uncorrected. Optical rotations were measured on a PerkinElmer Precisly/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at 20 °C. HPLC analyses were obtained using either a Shimadzu HPLC consisting of a DGU-20A5 degassing unit, LC-20AT liquid chromatography pump, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven; or a Shimadzu HPLC consisting of a DGU-20A5R degassing unit, LC-20AD liquid chromatography pump, SIL-20AHT autosampler, SPD-20A UV−vis detector and a CTO-20A column oven. Separation was achieved using DAICEL CHIRALPAK AS-H, AD-H, and IB columns, CHIRALCEL OD-H and OJ-H using the method stated. HPLC traces of enantiomerically enriched compounds were compared with authentic racemic spectra. ^{1}H, ^{13}C{^{1}H}, and ^{19}F{^{1}H} nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance II 400 (^{1}H 400 MHz; ^{13}C{^{1}H} 101 MHz; ^{19}F{^{1}H} 376 MHz) or a Bruker Avance II 500 (^{1}H 500 MHz; ^{13}C{^{1}H} 126 MHz; ^{19}F{^{1}H} 471 MHz) spectrometer at ambient temperature in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) and referenced to the residual solvent peak. All coupling constants, *J*, are quoted in Hz. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), tt (triplet of triplets), ddd (doublet of doublet of doublets), and m (multiplet). The abbreviation Ar is used to denote aromatic, Ph to denote phenyl, Bn to denote benzyl, br to denote broad, and app to denote apparent. NMR peak assignments were confirmed using 2D ^{1}H correlated spectroscopy (COSY), ^{1}H−^{13}C heteronuclear single quantum coherence (HSQC), and 2D ^{1}H−^{13}C heteronuclear multiple-bond correlation spectroscopy (HMBC) where necessary. Infrared spectra were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory (diamond puck). Spectra were recorded of either thin films or solids, with characteristic absorption wavenumbers (ν_{max}) reported in cm^{-1}. Mass spectrometry (HRMS) data were acquired by electrospray ionization (ESI) at either the University of St Andrews Mass Spectrometry Facility or at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

General Procedures. *General Experimental Procedure A: Synthesis of α-Silyl Acids.* According to a procedure reported by Rogers et al.,[19] diisopropylamine (9.6 mmol, 2.1 equiv) was dissolved in THF (10 mL) under an N_2-atmosphere. The solution was cooled to −78 °C and *n*-BuLi (9.6 mmol, 2.1 equiv) was added. The mixture was warmed to r.t. for 15 min before being cooled to −78 °C again. 2-(Trimethylsilyl) acetic acid (4.5 mmol, 1.0 equiv) was added and the mixture was stirred at 0 °C for 1 h, followed by 1.5 h at r.t. Subsequently the specified halide (4.7 mmol, 1.05 equiv) was added at 0 °C and the mixture was stirred additional 30 min at 0 °C. Then the reaction was quenched by the addition of HCl (1 M) and the pH adjusted to 2. The aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude residue was triturated from pentane to give the desired product.

General Experimental Procedure B: Synthesis of Alternative α-Silyl Acids. According to a procedure reported by Becker et al.,[20] to an oven-dried round-bottomed flask (250 mL) equipped with a magnetic stirring bar were added diisopropylamine (24.0 mmol, 1.15 equiv) and anhydrous THF (40 mL). The mixture was cooled to −78 °C, and then *n*-BuLi 1.6 M (24.0 mmol, 1.15 equiv) was added dropwise. The mixture was warmed to r.t. for 15 min and cooled again to −78 °C. Trimethylsilyl acetate ($CH_3CO_2SiMe_3$) (21.0 mmol, 1.0 equiv) was added dropwise to the cooled solution of LDA over 15 min and the reaction mixture was stirred for 2 h at −78 °C. Then chlorosilane (24.0 mmol, 1.15 equiv) in anhydrous THF (5 mL) was added dropwise to the solution over 10 min. The reaction mixture was then stirred at −78 °C for 2 additional hours and allowed to reach room temperature overnight. A solution of saturated aqueous NaCl solution (30 mL) was added, and the pH was adjusted to 3 using 1 M aqueous HCl. The aqueous layer was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual crude product was dissolved in THF (30 mL) and saturated aqueous NH_4Cl solution (20 mL) was added. The reaction mixture was then stirred at room temperature for 1 h. Afterward, the aqueous layer was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were washed with water (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was crystallized from hexane to give the desired product.

General Experimental Procedure C: Synthesis of Trifluoromethylenones. According to a procedure reported by Davies et al.,[9b] the requisite aldehyde (1.0 equiv), piperidine (1.0 equiv), and acetic acid (1.5 equiv) were dissolved in toluene (0.5 M) at 0 °C. A solution of trifluoromethyl ketone (2.0−4.0 equiv) in toluene (2−4 M) was added and the reaction was stirred for 2 h at 0 °C, followed by heating at 50 °C for 16 h. The reaction was cooled to r.t. and quenched with saturated aqueous NH_4Cl solution. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to leave the crude product, which was purified by flash column chromatography on silica.

General Experimental Procedure D: Synthesis of β-Lactones. In a flame-dried Schlenk tube under an N_2 atmosphere, *N*,*N*-diisopropylethylamine (3.0 equiv) and pivaloyl chloride (3.0 equiv) were added sequentially to a solution of appropriate acid (2.0 equiv) in anhydrous MTBE (0.1 M) at 0 °C. The mixture was allowed to stir for 15 min at 0 °C, followed by the sequential addition of the specified ketone (1.0 equiv), (2*S*,3*R*)-HyperBTM (5 mol %), and *N*,*N*-diisopropylethylamine (1.0 equiv). The mixture was allowed to stir for the specified time at r.t. The solvent was then removed under reduced pressure, and the crude residue purified by Biotage automated column chromatography in the stated solvent system to give the desired product.

(S,E)-4-Styryl-4-(trifluoromethyl)oxetan-2-one ***(3).*** Following General Procedure D, 2-(trimethylsilyl) acetic acid (66 mg, 0.5 mmol), *N*,*N*-diisopropylethylamine (132 μL, 0.75 mmol), pivaloyl chloride (92 μL, 0.75 mmol), and MTBE (3 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one (50 mg, 0.25 mmol), (2*S*,3*R*)-HyperBTM (4 mg, 12.5 μmol), and *N*,*N*-diisopropylethylamine (44 μL, 0.25 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 90:10 30 CV)], the title compound (45 mg, 75%) as a bright yellow oil. $[\alpha]_D^{20}$ −19.3 (*c* 1.4, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (99.3:0.7 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (major): 16.1 min, t_R (minor): 24.9 min, 92:8 er. IR ν_{max} (film) 1852 (C═O), 1167 (C−O), 972 (C═C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57−7.31 (5H, m, Ph*H*), 7.02 (1H, d, *J* 16.0, CH═C*H*Ph), 6.41 (1H, d, *J* 16.0, C*H*═CHPh), 3.90 (1H, d, *J* 16.4, C(3)H_AH_B), 3.64−3.59 (1H, dq, *J* 16.6, 2.2, C(3)H_AH_B). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −79.9 (CF_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C 163.6 (*C*(2)), 136.8 (*C*H═CHPh), 134.2 (PhC(1)), 129.5 (PhC(4)H), 128.9 (PhC(3,5)H), 127.2 (PhC(2,6)H), 123.3 (q, *J* 281.0, CF_3), 117.4 (CH═*C*HPh), 74.2 (q, *J* 34.2, *C*(4)), 46.0 (*C*(3)H_2). HRMS (ESI+) *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_9O_2F_3Na$ 265.0447, found 265.0445.

(S,E)-4-(4-Bromostyryl)-4-(trifluoromethyl)oxetan-2-one ***(7).*** Following General Procedure D, 2-(trimethylsilyl) acetic acid (66 mg, 0.5 mmol), *N*,*N*-diisopropylethylamine (132 μL, 0.75 mmol), pivaloyl chloride (92 μL, 0.75 mmol), and MTBE (3 mL) for 15 min, followed by (*E*)-4-(4-bromophenyl)-1,1,1-trifluorobut-3-en-2-one (70 mg, 0.25 mmol), (2*S*,3*R*)-HyperBTM (4 mg, 12.5 μmol), and *N*,*N*-diisopropylethylamine (44 μL, 0.25 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (63 mg, 78%) as a a white solid. mp 52−54 °C. $[\alpha]_D^{20}$ −33.2 (*c*, 0.5, $CHCl_3$). Chiral HPLC analysis, Chiralpak IB (99:1 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (major): 12.7 min, t_R (minor): 15.6 min, 92:8 er. IR ν_{max} (film) 1854 (C═O), 1165 (C−O), 972 (C═C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.56−7.53 (2H, m,

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ArC(3,5)*H*), 7.36−7.33 (2H, m, ArC(2,6)*H*), 6.97 (1H, d, *J* 16.0, CH=C*H*Ar), 6.39 (1H, d, *J* 16.0, C*H*=CHAr), 3.90 (1H, d, *J* 16.6, C(3)$H_A$$H_B$), 3.60 (1H, dq, *J* 16.5, 1.2, C(3)$H_A$$H_B$). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −79.9 (CF_3). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C 163.4 (*C*(2)), 135.6 (CH=CHAr), 133.2 (PhC(1)), 132.1 (ArC(3,5)H), 128.7 (ArC(2,6)H), 123.6 (ArC(4)), 123.1 (q, *J* 280.6, CF_3), 118.2 (CH=CHAr), 74.1 (q, *J* 34.2, *C*(4)), 46.1 (*C*(3)). HRMS (ESI+) *m*/*z* [M + OH]$^-$ calcd for $C_{12}H_9BrF_3O_3$ 336.9693 (−0.3 ppm), found 336.9692.

(S,E)-4-(2-Bromostyryl)-4-(trifluoromethyl)oxetan-2-one ***(8)***. Following General Procedure D, 2-(trimethylsilyl) acetic acid (66 mg, 0.5 mmol), *N*,*N*-diisopropylethylamine (132 μL, 0.75 mmol), pivaloyl chloride (92 μL, 0.75 mmol), and MTBE (3 mL) for 15 min, followed by (*E*)-4-(2-bromophenyl)-1,1,1-trifluorobut-3-en-2-one (70 mg, 0.25 mmol), (2*S*,3*R*)-HyperBTM (4 mg, 12.5 μmol), and *N*,*N*-diisopropylethylamine (44 μL, 0.25 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (61 mg, 76%) as a bright yellow oil. $[\alpha]_D^{20}$ −16.8 (*c*, 0.5, $CHCl_3$). Chiral HPLC analysis, Chiralpak IB (99:1 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 13.5 min, t_R (major): 16.6 min, 90:10 er. IR ν_{max} (film) 1852 (C=O), 1167 (C−O), 970 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.64−7.62 (1H, m, ArC(3)*H*), 7.57−7.55 (1H, m, ArC(5)*H*), 7.38 (1H, d, *J* 16.0, CH=C*H*Ar), 7.38−7.34 (1H, m, ArC(4)*H*), 7.26−7.22 (1H, m, ArC(6)*H*), 6.36 (1H, d, *J* 16.2, C*H*=CHAr), 3.92 (1H, d, *J* 16.6, C(3)$H_A$$H_B$), 3.67 (1H, dq, *J* 16.6, 1.1, C(3)$H_A$$H_B$). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −79.8 (CF_3). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C 163.4 (*C*(2)), 136.0 (CH=CHAr), 134.4 (Ar*C*(1)), 133.3 (ArC(3)H), 130.7 (Ar*C*(5)H), 127.8 (Ar*C*(6)H), 127.5 (Ar*C*(4)H), 124.3 (Ar*C*(2)), 123.2 (q, *J* 282.1, CF_3), 120.5 (CH=CHAr), 74.1 (q, *J* 34.6, *C*(4)), 45.9 (*C*(3)H_2). HRMS (ESI+) *m*/*z* [M + OH]$^-$ calcd for $C_{12}H_9BrF_3O_3$ 336.9693, found 336.9694.

(S,E)-4-(3-Methoxystyryl)-4-(trifluoromethyl)oxetan-2-one ***(9)***. Following General Procedure D, 2-(trimethylsilyl) acetic acid (66 mg, 0.5 mmol), *N*,*N*-diisopropylethylamine (132 μL, 0.75 mmol), pivaloyl chloride (92 μL, 0.75 mmol), and MTBE (3 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-(3-methoxyphenyl)but-3-en-2-one (58 mg, 0.25 mmol), (2*S*,3*R*)-HyperBTM (4 mg, 12.5 μmol), and *N*,*N*-diisopropylethylamine (44 μL, 0.25 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (44 mg, 65%) as a bright yellow oil. $[\alpha]_D^{20}$ −7.6 (*c*, 0.2, $CHCl_3$). Chiral HPLC analysis, Chiralpak AS-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 11.1 min, t_R (major): 15.3 min, 89:11 er; IR ν_{max} (film) 1856 (C=O), 1165 (C−O), 974 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.35−7.31 (1H, m, ArC(5)*H*), 7.08−7.06 (1H, m, ArC(6)*H*), 6.99 (1H, d, *J* 16.0, CH=C*H*Ph), 6.99−6.98 (1H, m, ArC(2)*H*), 6.95−6.92 (1H, m, ArC(4)*H*), 6.39 (1H, d, *J* 16.0, C*H*=CHAr), 3.90 (1H, d, *J* 16.5, C(3)$H_A$$H_B$), 3.86 (3H, s, OC$H_3$), 3.61 (1H, dq, *J* 16.5, 1.1, C(3)$H_A$$H_B$). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −79.8 (CF_3). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C 163.6 (*C*(2)), 160.0 Ar*C*(3)), 136.7 (CH=CHAr), 135.6 (Ar*C*(1)), 130.0 (Ar*C*(5)H), 123.2 (q, *J* 281.2, CF_3), 119.7 (Ar*C*(6)H), 117.7 (CH=CHPh), 115.2 (Ar*C*(4)H), 112.4 (Ar*C*(2)H), 74.2 (q, *J* 34.4, *C*(4)), 55.4 (O*C*H_3), 46.0 (*C*(3)H_2). HRMS (ESI+) *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{11}F_3NaO_3$ 295.0552, found 295.0548.

(S,E)-4-(1-Phenylprop-1-en-2-yl)-4-(trifluoromethyl)oxetan-2-one ***(10)***. Following General Procedure D, 2-(trimethylsilyl)acetic acid (53 mg, 0.4 mmol), *N*,*N*-diisopropylethylamine (105 μL, 0.6 mmol), pivaloyl chloride (66 μL, 0.6 mmol), and MTBE (2 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-3-methyl-4-phenylbut-3-en-2-one (40 mg, 0.2 mmol), (2*S*,3*R*)-HyperBTM (3 mg, 10.0 μmol), and *N*,*N*-diisopropylethylamine (35 μL, 0.2 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 10 g, 36 mL min^{-1}, petrol:Et_2O (99:1 4 CV, 99:1 to 90:10 20 CV)], the title compound (41 mg, 80%) as a colorless oil. $[\alpha]_D^{20}$ −1.6 (*c*, 0.5, $CHCl_3$). Chiral HPLC analysis, Chiralcel OJ-H (99.8:0.2 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 34.5 min, t_R (major): 38.3 min, 92:8 er. IR ν_{max} (film) 1852 (C=O), 1175 (C−O). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.44−7.41 (2H, m, Ph*H*), 7.35−7.33 (3H, m, Ar*H*), 6.84 (1H, s, C*H*Ph), 3.90 (1H, d, *J* 16.6, C(3)$H_A$$H_B$), 3.64 (1H, dq, *J* 16.5, 1.1, C(3)$H_A$$H_B$), 2.06 (3H, m, C$H_3$). ^{19}F NMR (471 MHz, $CDCl_3$) δ_F −78.2 (s, CF_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C 163.9 (CO), 135.2 (PhC(1)), 132.9 (ArCH), 129.1 (PhC(3,5)H), 128.5 (PhC(2,6)H), 128.0 (PhC(4)H), 127.8 (PhCH=CCH$_3$), 123.6 (q, *J* 284.6, CF_3), 76.8 (q, *J* 32.9, CCF$_3$), 45.4 (C(3)), 14.2 (CH_3). HRMS (ESI+) *m*/*z* [M + OH]$^-$ calcd for $C_{13}H_{12}F_3O_3$ 273.0744, found 273.0742.

(S,E)-4-(1-(4-Bromophenyl)prop-1-en-2-yl)-4-(trifluoromethyl)-oxetan-2-one ***(11)***. Following General Procedure D, 2-(trimethylsilyl)acetic acid (265 mg, 2.0 mmol), *N*,*N*-diisopropylethylamine (522 μL, 3.0 mmol), pivaloyl chloride (367 μL, 3.0 mmol), and MTBE (5 mL) for 15 min, followed by (*E*)-4-(4-bromophenyl)-1,1,1-trifluoro-3-methylbut-3-en-2-one (293 mg, 1.0 mmol), (2*S*,3*R*)-HyperBTM (15 mg, 100.0 μmol), and *N*,*N*-diisopropylethylamine (241 μL, 1.5 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 10 g, 36 mL min^{-1}, petrol:Et_2O (99:1 4 CV, 99:1 to 90:10 30 CV)], the title compound (288 mg, 86%) as a colorless oil; $[\alpha]_D^{20}$ +1.0 (*c*, 0.4, $CHCl_3$); Chiral HPLC analysis, Chiralpak AS-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 7.9 min, t_R (major): 9.7 min, 94:6 er; IR ν_{max} (film) 1848 (C=O), 1173 (C−O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.56−7.53 (2H, m, ArC(3,5)*H*), 7.22−7.19 (2H, m, ArC(2,6)*H*), 6.77 (1H, s, C*H*Ar), 3.90 (1H, d, *J* 16.4, C(3)$H_A$$H_B$), 3.64−3.60 (1H, dq, *J* 16.5, 1.1, C(3)$H_A$$H_B$), 2.02 (3H, t, *J* 1.2, CH_3). ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −78.2 (s, CF_3). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C 163.7 (CO), 134.1 (Ar*C*(1)), 131.7 (ArCH=CCH$_3$, Ar*C*(3,5)H), 130.7 (Ar*C*(2,6)H), 128.6 (ArCH=CCH$_3$), 123.5 (q, *J* 282.9, CF_3), 122.1 (Ar*C*(4)), 76.7 (q, *J* 33.2, CCF$_3$), 45.4 (C(3)), 14.2 (CH_3). HRMS (ESI+) *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}BrF_3O_2$ 334.9889, found 334.9888.

(S,E)-4-(1-(4-Methoxyphenyl)prop-1-en-2-yl)-4-(trifluoromethyl)-oxetan-2-one ***(12)***. Following General Procedure D, 2-(trimethylsilyl)acetic acid (106 mg, 0.8 mmol), *N*,*N*-diisopropylethylamine (210 μL, 1.2 mmol), pivaloyl chloride (132 μL, 1.2 mmol), and MTBE (4 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-(4-methoxyphenyl)-3-methylbut-3-en-2-one (98 mg, 0.4 mmol), (2*S*,3*R*)-HyperBTM (6 mg, 20.0 μmol), and *N*,*N*-diisopropylethylamine (70 μL, 0.4 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 10 g, 36 mL min^{-1}, petrol:Et_2O (99:1 4 CV, 99:1 to 90:10 30 CV)], the title compound (60 mg, 52%) as a colorless oil; $[\alpha]_D^{20}$ +8.0 (*c*, 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C), t_R (minor): 29.0 min, t_R (major): 35.4 min, 93:7 er; IR ν_{max} (film) 1850 (C=O), 1175 (C−O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.32−7.28 (2H, m, ArC(2,6)*H*), 6.96−6.93 (2H, m, ArC(3,5)*H*), 6.75 (1H, s, C*H*Ph), 3.88 (1H, d, *J* 16.4, C(3)$H_A$$H_B$), 3.86 (3H, s, OC$H_3$), 3.64−3.59 (1H, dq, *J* 16.4, 1.1, C(3)$H_A$$H_B$), 2.06 (3H, t, *J* 1.2, CH_3). ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −78.3 (s, CF_3). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C 163.9 (CO), 159.3 (Ar*C*(4)), 132.3 (ArCH=CCH$_3$), 130.6 (Ar*C*(2,6)H), 127.8 (PhCH=CCH$_3$), 125.7 (PhC(1)), 123.6 (q, *J* 282.6, CF_3), 113.9 (Ar*C*(3,5)H), 76.9 (q, *J* 32.2, CCF$_3$), 55.3 (OCH$_3$), 45.3 (C(3)), 14.2 (CH_3). HRMS (ESI+) *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}F_3O_3$ 287.0890, found 287.0887.

(S,E)-4-(1,2-Diphenylvinyl)-4-(trifluoromethyl)oxetan-2-one ***(13)***. Following General Procedure D, 2-(trimethylsilyl) acetic acid (105 mg, 0.8 mmol), *N*,*N*-diisopropylethylamine (210 μL, 1.2 mmol), pivaloyl chloride (132 μL, 1.2 mmol), and MTBE (4.5 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-3,4-diphenylbut-3-en-2-one (110 mg, 0.4 mmol), (2*S*,3*R*)-HyperBTM (6 mg, 20.0 μmol), and *N*,*N*-diisopropylethylamine (71 μL, 0.4 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (117 mg, 92%) as a colorless oil; $[\alpha]_D^{20}$ +2.1 (*c*, 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (99:1 hexane:IPA, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C), t_R (major): 12.6 min, t_R (minor): 14.5 min, 93:7 er; IR ν_{max} (film) 1854 (C=O), 1152 (C−O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.43−7.41 (3H, m, CHPhC(2,4,6)), 7.26−7.23 (2H, m, CHPhC(3,5)), 7.22−7.15 (3H, m, CPhC(3,4,5)*H*), 7.09

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(1H, s, PhC*H*=C), 6.97−6.94 (2H, m, CPhC(2,6)*H*), 3.82 (1H, d, *J* 16.8, C(3) H_AH_B), 3.75 (1H, d, *J* 16.8, C(3)H_AH_B). ^{19}F NMR (471 MHz, $CDCl_3$) δ_F −76.6 (CF_3). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C 163.8 (*C*(2)), 135.1 (*C*HPh), 134.9 (*C*Ph), 134.4 (CPh*C*(1)), 131.6 (CHPh*C*(1)), 129.9 (CPh*C*(3,5)H), 129.7 (CHPh*C*(3,5)H), 129.2 (CHPh*C*(2,6)H), 128.7 (CPh*C*(4)H), 128.5 (CHPh*C*(4)H), 128.2 (CPh*C*(2,6)H), 123.5 (q, *J* 281.7, CF_3), 76.3 (q, *J* 33.0, *C*(4)), 45.6 (*C*(3)). HRMS (ESI+) *m/z* [M + OH]$^-$ calcd for $C_{18}H_{14}F_3O_3$ 335.0901, found 335.0902.

(3S,4R)-3-Methyl-4-((E)-styryl)-4-(trifluoromethyl)oxetan-2-one ***(15)***. Following General Procedure D, 2-(trimethylsilyl)propanoic acid (73 mg, 0.5 mmol), *N,N*-diisopropylethylamine (132 μL, 0.75 mmol), pivaloyl chloride (92 μL, 0.75 mmol), and MTBE (3 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one (50 mg, 0.25 mmol), (2*S*,3*R*)-HyperBTM (4 mg, 12.5 μmol), and *N,N*-diisopropylethylamine (44 μL, 0.25 mmol) for 20 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 95:5 40 CV)], the title compound (48 mg, 75%) as a colorless oil; $[\alpha]_D^{20}$ −118.4 (*c* 1.1, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (99.5:0.5 hexane:IPA, flow rate 0.7 mL min^{-1}, 211 nm, 30 °C), major diastereoisomer: t_R (minor): 7.4 min, t_R (major): 8.7 min, 94:6 er; minor diastereoisomer: t_R (major): 12.1 min, t_R (minor): 13.9 min, 77:23 er; IR ν_{max} (film) 1852 (C=O), 1165 (C−O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.50−7.48 (2H, m, PhC(2,6)*H*), 7.47−7.40 (3H, m, PhC(3,4,5)*H*), 7.05 (1H, d, *J* 16.0, CH=C*H*Ph), 6.21 (1H, d, *J* 16.0, C*H*=CHPh), 4.10 (1H, q, *J* 7.7, C(3)*H*), 1.36 (3H, d, *J* 7.7, C(3)CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −79.7 (CF_3). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C 163.6 (*C*(2)), 136.8 (CH=CHPh), 134.2 (Ph*C*(1)), 129.5 (Ph*C*(4)H), 128.9 (Ph*C*(3,5)H), 127.2 (Ph*C*(2,6)H), 123.3 (q, *J* 281.0, *C*F$_3$), 117.4 (CH=CHPh), 78.3 (q, *J* 33.2, *C*(4)), 52.0 (*C*(3)H), 9.7 (C(3)CH_3); HRMS (ESI+) *m/z* [M + H]$^+$ calcd for $C_{13}H_{12}F_3O_2$ 257.0784, found 257.0784.

(3S,4R)-4-((E)-4-Fluorostyryl)-3-methyl-4-(trifluoromethyl)-oxetan-2-one ***(16)***. Following General Procedure D, 2-(trimethylsilyl)propanoic acid (117 mg, 0.8 mmol), *N,N*-diisopropylethylamine (210 μL, 1.2 mmol), pivaloyl chloride (132 μL, 1.2 mmol), and MTBE (4.5 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-(4-fluorophenyl)but-3-en-2-one (87 mg, 0.4 mmol), (2*S*,3*R*)-HyperBTM (6 mg, 20.0 μmol), and *N,N*-diisopropylethylamine (71 μL, 0.4 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (77 mg, 70%) as a colorless oil; $[\alpha]_D^{20}$ −102.9 (*c*, 0.1, $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R(minor): 15.3 min, t_R(major): 25.6 min, 99:1 er; IR ν_{max} (film) 1850 (C=O), 1161 (C−O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.49−7.45 (2H, m, ArC(2,6)*H*), 7.12−7.08 (2H, m, ArC(3,5)*H*), 7.01 (1H, d, *J* 16.0, ArC*H*=CH), 6.12 (1H, d, *J* 16.1, ArCH=C*H*), 4.10 (1H, q, *J* 7.7, C(3)*H*), 1.35 (3H, d, *J* 7.7, C(3)CH_3). ^{19}F NMR (471 MHz, $CDCl_3$) δ_F −79.7 (C*F*$_3$), −111.4 (Ar*F*). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C 167.9 (*C*(2)), 163.3 (d, *J* 247.9, Ar*C*(4)), 136.5 (ArCH=CH), 130.7 (d, *J* 3.3, Ar*C*(1)), 128.8 (Ar*C*(2,6)H), 123.4 (q, *J* 282.0, CF_3), 116.0 (d, *J* 21.8, Ar*C*(3,5)H), 114.7 (ArCH=CH), 78.2 (q, *J* 33.2, *C*(4)), 52.0 (*C*(3)), 9.7 (CCH_3). HRMS (ESI+) *m/z* [M + OH]$^-$ calcd for $C_{13}H_{11}F_4O_3$ 291.0650, found 291.0650.

(3S,4R)-4-((E)-4-Chlorostyryl)-3-methyl-4-(trifluoromethyl)-oxetan-2-one ***(17)***. Following General Procedure D, 2-(trimethylsilyl)propanoic acid (117 mg, 0.8 mmol), *N,N*-diisopropylethylamine (210 μL, 1.2 mmol), pivaloyl chloride (132 μL, 1.2 mmol), and MTBE (4.5 mL) for 15 min, followed by (*E*)-4-(4-chlorophenyl)-1,1,1-trifluorobut-3-en-2-one (94 mg, 0.4 mmol), (2*S*,3*R*)-HyperBTM (6 mg, 20.0 μmol), and *N,N*-diisopropylethylamine (71 μL, 0.4 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (88 mg, 76%) as a colorless solid; mp 70−72 °C; $[\alpha]_D^{20}$ −108.7 (*c*, 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 22.4 min, t_R (major): 34.0 min, 99:1 er; IR ν_{max} (film) 1840 (C=O), 1159 (C−O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.44−7.36 (4H, m, Ar*H*), 7.01 (1H, d, *J* 16.1, ArC*H*=CH), 6.18 (1H, d, *J* 16.1, ArCH=C*H*), 4.11 (1H, q, *J* 7.7, C(3)*H*), 1.35 (3H, d, *J* 7.7, C(3)CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −79.6 (C*F*$_3$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C 167.8 (*C*(2)), 136.4 (ArCH=CH), 135.2 (Ar*C*(4)), 133.0 (Ar*C*(1)), 129.1 (Ar*C*(3,5)H), 128.3 (Ar*C*(2,6)H), 123.4 (q, *J* 280.5, *C*F$_3$), 115.6 (ArCH=CH), 78.2 (q, *J* 33.5, *C*(4)), 52.1 (*C*(3)), 9.7 (CCH_3). HRMS (ESI+) *m/z* [M + OH]$^-$ calcd for $C_{13}H_{11}ClF_3O_3$ 307.0354, found 307.0359.

(3S,4R)-4-((E)-4-Bromostyryl)-3-methyl-4-(trifluoromethyl)-oxetan-2-one ***(18)***. Following General Procedure D, 2-(trimethylsilyl)propanoic acid (117 mg, 0.8 mmol), *N,N*-diisopropylethylamine (210 μL, 1.2 mmol), pivaloyl chloride (132 μL, 1.2 mmol), and MTBE (4.5 mL) for 15 min, followed by (*E*)-4-(4-bromophenyl)-1,1,1-trifluorobut-3-en-2-one (112 mg, 0.4 mmol), (2*S*,3*R*)-HyperBTM (6 mg, 20.0 μmol), and *N,N*-diisopropylethylamine (71 μL, 0.4 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (93 mg, 69%) as a white solid; mp 74−76 °C; $[\alpha]_D^{20}$ −107.3 (*c*, 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 28.6 min, t_R (major): 42.1 min, >99:1 er; IR ν_{max} (film) 1836 (C=O), 1157 (C−O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.56−7.52 (2H, m, ArC(3,5)*H*), 7.37−7.33 (2H, m, ArC(2,6)*H*), 6.99 (1H, d, *J* 16.0, ArC*H*=CH), 6.20 (1H, d, *J* 16.0, ArCH=C*H*), 4.11 (1H, q, *J* 7.7, C(3)*H*), 1.35 (3H, d, *J* 7.7, C(3)CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −79.6 (C*F*$_3$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C 167.8 (*C*(2)), 136.5 (ArCH=CH), 133.4 (Ar*C*(4)), 132.1 (Ar*C*(3,5)H), 128.6 (Ar*C*(2,6)H), 123.4 (Ar*C*(1)), 123.3 (q, *J* 280.5, *C*F$_3$), 115.8 (ArCH=*C*H), 78.2 (q, *J* 33.6, *C*(4)), 52.1 (*C*(3)), 9.7 (CCH_3). HRMS (ESI+) *m/z* [M + OH]$^-$ calcd for $C_{13}H_{11}BrF_3O_3$ 350.9849, found 350.9851.

(3S,4R)-3-Methyl-4-(trifluoromethyl)-4-((E)-4-(trifluoromethyl)-styryl)oxetan-2-one ***(19)***. Following General Procedure D, 2-(trimethylsilyl)propanoic acid (73 mg, 0.5 mmol), *N,N*-diisopropylethylamine (132 μL, 0.75 mmol), pivaloyl chloride (83 μL, 0.75 mmol), and MTBE (3 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one (67 mg, 0.25 mmol), (2*S*,3*R*)-HyperBTM (3.75 mg, 12.6 μmol), and *N,N*-diisopropylethylamine (45 μL, 0.25 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (51 mg, 62%) as a pale yellow solid; mp 48−50 °C; $[\alpha]_D^{20}$ −86.0 (*c*, 0.6, $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 18.1 min, t_R (major): 20.7 min, 99:1 er; IR ν_{max} (film) 1852 (C=O), 1163 (C−O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67 (2H, d, *J* 8.2, ArC(3,5)*H*), 7.59 (2H, d, *J* 8.4, C(2,6)*H*), 7.10 (1H, d, *J* 16.0, ArC*H*=CH), 6.31 (1H, d, *J* 16.0, ArCH=C*H*), 4.14 (1H, q, *J* 7.7, C(3)*H*), 1.37 (3H, d, *J* 7.7, C(3)CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −62.8 (ArC*F*$_3$), −79.5 (C*F*$_3$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C 167.6 (*C*(2)), 137.8 (Ar*C*(1)), 136.3 (ArCH=CH), 131.1 (q, *J* 32.6, Ar*C*(4)), 127.4 (Ar*C*(2,6)H), 125.9 (q, *J* 3.5, Ar*C*(3,5)H), 124.1 (q, *J* 271.6, ArC*F*$_3$), 123.3 (q, *J* 282.0, *C*F$_3$), 117.8 (ArCH=CH), 78.2 (q, *J* 33.4, *C*(4)), 52.2 (*C*(3)), 9.7 (CCH_3). HRMS (ESI+) *m/z* [M + OH]$^-$ calcd for $C_{14}H_{11}F_6O_3$ 341.0618, found 341.0617.

(3S,4R)-4-((E)-3-Methoxystyryl)-3-methyl-4-(trifluoromethyl)-oxetan-2-one ***(20)***. Following General Procedure D, 2-(trimethylsilyl)propanoic acid (117 mg, 0.8 mmol), *N,N*-diisopropylethylamine (210 μL, 1.2 mmol), pivaloyl chloride (132 μL, 1.2 mmol), and MTBE (4.5 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-(3-methoxyphenyl)but-3-en-2-one (92 mg, 0.4 mmol), (2*S*,3*R*)-HyperBTM (6 mg, 20.0 μmol), and *N,N*-diisopropylethylamine (71 μL, 0.4 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (58 mg, 51%) as a colorless oil; $[\alpha]_D^{20}$ −90.5 (*c*, 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 21.5 min, t_R (major): 33.8 min, >99:1 er; IR ν_{max} (film) 1850 (C=O), 1163 (C−O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33

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(1H, t, *J* 7.9, ArC(5)*H*), 7.08 (1H, d, *J* 7.6, ArC(6)*H*), 7.02 (1H, d, *J* 16.0, ArC*H*=CH), 7.00 (1H, m, ArC(2)*H*), 6.92 (1H, dd, *J* 8.3, 2.4 ArC(4)*H*), 6.19 (1H, d, *J* 16.0, ArCH=C*H*), 4.10 (1H, q, *J* 7.8, C(3)*H*), 3.87 (3H, s, OCH_3), 1.35 (3H, d, *J* 7.7, C(3)CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −79.7 (CF_3). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C 168.0 (*C*(2)), 160.0 (Ar*C*(3)), 137.6 (ArCH=CH), 135.9 (Ar*C*(1)), 129.9 (Ar*C*(5)H), 123.4 (q, *J* 280.5, CF_3), 119.6 (ArCH=CH), 115.3 (Ar*C*(6)H), 114.9 (Ar*C*(4)H), 112.5 (Ar*C*(2)-H), 78.2 (q, *J* 33.3, *C*(4)), 55.4 (OCH_3), 52.1 (*C*(3)), 9.7 (CCH_3). HRMS (ESI+) *m*/*z* [M + OH]$^-$ calcd for $C_{14}H_{14}F_3O_4$ 303.0850, found 303.0846.

(3S,4R)-3-Methyl-4-((E)-3-methylstyryl)-4-(trifluoromethyl)-oxetan-2-one ***(21)***. Following General Procedure D, 2-(trimethylsilyl)propanoic acid (117 mg, 0.8 mmol), *N*,*N*-diisopropylethylamine (210 μL, 1.2 mmol), pivaloyl chloride (132 μL, 1.2 mmol), and MTBE (4.5 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-(m-tolyl)but-3-en-2-one (86 mg, 0.4 mmol), (2*S*,3*R*)-HyperBTM (6 mg, 20.0 μmol), and *N*,*N*-diisopropylethylamine (71 μL, 0.4 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (71 mg, 66%) as a white solid; mp 34−35 °C; $[\alpha]_D^{20}$ −118.1 (*c*, 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 10.2 min, t_R (major): 15.2 min, >99:1 er; IR ν_{max} (film) 1852 (C=O), 1161 (C−O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.31−7.29 (3H, m, ArC(2,5,6)*H*), 7.21−7.19 (1H, m, ArC(4)*H*), 7.02 (1H, d, *J* 16.0, ArC*H*=CH), 6.19 (1H, d, *J* 16.0, ArCH=C*H*), 4.09 (1H, q, *J* 7.7, C(3)*H*), 3.40 (3H, s, $ArCH_3$), 1.35 (3H, d, *J* 7.7, C(3)CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −79.7 (CF_3). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C 168.1 (*C*(2)), 138.6 (Ar*C*(1)), 137.7 (ArCH=CH), 134.5 (Ar*C*(3)), 130.1 (Ar*C*(5)H), 128.8 (Ar*C*(4)H), 127.7 (ArCH=CH), 124.3 (Ar*C*(2)H), 123.4 (q, *J* 281.2, CF_3), 114.7 (Ar*C*(6)H), 78.3 (q, *J* 33.5, *C*(4)), 52.0 (*C*(3)), 21.4 ($ArCH_3$), 9.7 (CCH_3). HRMS (ESI+) *m*/*z* [M + OH]$^-$ calcd for $C_{14}H_{14}F_3O_3$ 287.0901, found 287.0901.

(3S,4R)-4-((E)-3-Bromostyryl)-3-methyl-4-(trifluoromethyl)-oxetan-2-one ***(22)***. Following General Procedure D, 2-(trimethylsilyl)propanoic acid (117 mg, 0.8 mmol), *N*,*N*-diisopropylethylamine (210 μL, 1.2 mmol), pivaloyl chloride (132 μL, 1.2 mmol), and MTBE (4.5 mL) for 15 min, followed by (*E*)-4-(3-bromophenyl)-1,1,1-trifluorobut-3-en-2-one (112 mg, 0.4 mmol), (2*S*,3*R*)-HyperBTM (6 mg, 20.0 μmol), and *N*,*N*-diisopropylethylamine (71 μL, 0.4 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (84 mg, 63%) as a colorless oil; $[\alpha]_D^{20}$ −95.3 (*c*, 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 24.2 min, t_R (major): 43.1 min, 99:1 er; IR ν_{max} (film) 1850 (C=O), 1163 (C−O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.65−7.64 (1H, m, ArC(6)*H*), 7.52−7.49 (1H, m, ArC(2)*H*), 7.40−7.38 (1H, m, ArC(4)*H*), 7.30−7.26 (1H, m, C(5)*H*), 6.99 (1H, d, *J* 16.0, ArC*H*=CH), 6.21 (1H, d, *J* 16.0, ArCH=C*H*), 4.12 (1H, q, *J* 7.7, C(3)*H*), 1.36 (3H, d, *J* 7.8, C(3)CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −79.6 (CF_3). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C 167.7 (*C*(2)), 136.6 (Ar*C*(1)), 136.3 (ArCH=CH), 132.2 (Ar*C*(4)H), 130.4 (Ar*C*(2)H), 129.7 (Ar*C*(5)H), 126.0 (Ar*C*(6)H), 123.3 (q, *J* 280.8, CF_3), 123.1 (Ar*C*(3)), 116.7 (ArCH=CH), 78.2 (q, *J* 33.5, *C*(4)), 52.2 (*C*(3)), 9.7 (CCH_3). HRMS (ESI+) *m*/*z* [M + OH]$^-$ calcd for $C_{13}H_{11}BrF_3O_3$ 350.9849, found 350.9846.

(3S,4R)-3-Methyl-4-((E)-2-(naphthalen-2-yl)vinyl)-4-(trifluoromethyl)oxetan-2-one ***(23)***. Following General Procedure D, 2-(trimethylsilyl)propanoic acid (117 mg, 0.8 mmol), *N*,*N*-diisopropylethylamine (210 μL, 1.2 mmol), pivaloyl chloride (132 μL, 1.2 mmol), and MTBE (4.5 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-(naphthalen-2-yl)but-3-en-2-one (100 mg, 0.4 mmol), (2*S*,3*R*)-HyperBTM (6 mg, 20.0 μmol), and *N*,*N*-diisopropylethylamine (71 μL, 0.4 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (66 mg, 54%) as a pale yellow solid; mp 102−104 °C; $[\alpha]_D^{20}$ −73.0 (*c*, 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 20.7 min, t_R (major): 40.4 min, >99:1 er; IR ν_{max} (film) 1846 (C=O), 1144 (C−O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.89−7.85 (4H, m, ArC(1,4,6,9)*H*), 7.65 (1H, dd, *J* 8.8, 1.7, ArC(3)*H*), 7.55−7.53 (2H, m, ArC(7,8)*H*), 7.22 (1H, d, *J* 16.0, ArC*H*=CH), 6.32 (1H, d, *J* 16.0, ArCH=C*H*), 4.13 (1H, q, *J* 7.7, C(3)*H*), 1.39 (3H, d, *J* 7.7, C(3)CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −79.6 (CF_3). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C 168.0 (*C*(2)), 137.7 (ArCH=CH), 133.7 (Ar*C*(4a)), 133.4 (Ar*C*(2)), 131.9 (Ar*C*(5)H), 128.7 (Ar*C*(4)H), 128.3 (Ar*C*(8a)), 128.2 (Ar*C*(1)H), 127.8 (Ar*C*(6)H), 126.9 (ArCH=CH), 126.8 (Ar*C*(8)-H), 123.5 (q, *J* 281.8, CF_3), 123.2 (Ar*C*(7)H), 115.1 (Ar*C*(3)), 78.4 (q, *J* 33.7, *C*(4)), 52.1 (*C*(3)), 9.8 (CCH_3). HRMS (ESI+) *m*/*z* [M + OH]$^-$ calcd for $C_{17}H_{14}F_3O_3$ 323.0901, found 323.0900.

(3S,4R)-3-Methyl-4-((E)-2-(naphthalen-1-yl)vinyl)-4-(trifluoromethyl)oxetan-2-one ***(24)***. Following General Procedure D, 2-(trimethylsilyl)propanoic acid (117 mg, 0.8 mmol), *N*,*N*-diisopropylethylamine (210 μL, 1.2 mmol), pivaloyl chloride (132 μL, 1.2 mmol), and MTBE (4.5 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-(naphthalen-1-yl)but-3-en-2-one (100 mg, 0.4 mmol), (2*S*,3*R*)-HyperBTM (6 mg, 20.0 μmol), and *N*,*N*-diisopropylethylamine (71 μL, 0.4 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (76 mg, 62%) as a white solid; mp 56−58 °C; $[\alpha]_D^{20}$ −24.9 (*c*, 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C), t_R (minor): 23.3 min, t_R (major): 32.8 min, >99:1 er; IR ν_{max} (film) 1848 (C=O), 1159 (C−O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.10 (1H, m, ArC(4)*H*), 7.93−7.90 (2H, m, ArC(5,8)*H*), 7.85 (1H, d, *J* 15.8, ArC*H*=CH), 7.66 (1H, dt, *J* 7.1, 0.9, ArC(2)*H*), 7.63−7.55 (2H, m, ArC(3,7)*H*), 7.53−7.50 (1H, m, ArC(6)*H*), 6.27 (1H, d, *J* 15.8, ArCH=C*H*), 4.16 (1H, q, *J* 7.7, C(3)*H*), 1.44 (3H, d, *J* 7.7, C(3)CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −79.6 (CF_3). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C 168.0 (*C*(2)), 135.4 (ArCH=CH), 133.6 (Ar*C*(1)), 132.5 (Ar*C*(4a)), 131.0 (Ar*C*(8a)), 129.6 (Ar*C*(5)H), 128.7 (Ar*C*(4)H), 126.8 (Ar*C*(3)H), 126.3 (Ar*C*(7)H), 125.5 (Ar*C*(6)H), 124.4 (Ar*C*(8)H), 123.47 (q, *J* 281.9, CF_3), 123.45 (Ar*C*(2)H), 118.4 (ArCH=CH), 78.3 (q, *J* 32.9, *C*(4)), 52.1 (*C*(3)), 9.9 (CCH_3). HRMS (ESI+) *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}F_3O_2$ 307.0940, found 307.0936.

(3S,4R)-4-((E)-2-Bromostyryl)-3-methyl-4-(trifluoromethyl)-oxetan-2-one ***(25)***. Following General Procedure D, 2-(trimethylsilyl)propanoic acid (117 mg, 0.8 mmol), *N*,*N*-diisopropylethylamine (210 μL, 1.2 mmol), pivaloyl chloride (132 μL, 1.2 mmol), and MTBE (4.5 mL) for 15 min, followed by (*E*)-4-(2-bromophenyl)-1,1,1-trifluorobut-3-en-2-one (111 mg, 0.4 mmol), (2*S*,3*R*)-HyperBTM (6 mg, 20.0 μmol), and *N*,*N*-diisopropylethylamine (71 μL, 0.4 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (80 mg, 60%) as a colorless oil; $[\alpha]_D^{20}$ −29.6 (*c*, 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (99.9:0.1 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 12.0 min, t_R (major): 15.0 min, 99:1 er; IR ν_{max} (film) 1852 (C=O), 1165 (C−O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.63 (1H, dd, *J* 8.0, 1.3, ArC(3)*H*), 7.55 (1H, dd, *J* 7.8, 1.7, ArC(5)*H*), 7.39 (1H, d, *J* 16.0, ArC*H*=CH), 7.36 (1H, td, *J* 7.5, 1.3, ArC(4)*H*), 7.24 (1H, td, *J* 7.8, 1.8, ArC(6)*H*), 6.15 (1H, d, *J* 16.0, ArCH=C*H*), 4.12 (1H, q, *J* 7.7, C(3)*H*), 1.39 (3H, d, *J* 7.7, C(3)CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −79.5 (CF_3). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C 167.8 (*C*(2)), 136.9 (ArCH=CH), 135.0 (Ar*C*(1)), 133.3 (Ar*C*(3)-H), 130.4 (Ar*C*(5)H), 127.7 (Ar*C*(6)H), 127.5 (Ar*C*(4)H), 124.1 (Ar*C*(2)), 123.2 (q, *J* 282.2, CF_3), 118.4 (ArCH=CH), 78.1 (q, *J* 33.6, *C*(4)), 52.1 (*C*(3)), 9.9 (CCH_3). HRMS (ESI+) *m*/*z* [M + OH]$^-$ calcd for $C_{13}H_{11}F_3BrO_3$ 350.9849, found 350.9848.

(3S,4R)-3-Methyl-4-((E)-2-methylstyryl)-4-(trifluoromethyl)-oxetan-2-one ***(26)***. Following General Procedure D, 2-(trimethylsilyl)propanoic acid (117 mg, 0.8 mmol), *N*,*N*-diisopropylethylamine (210 μL, 1.2 mmol), pivaloyl chloride (132 μL, 1.2 mmol), and MTBE (4.5 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-(o-tolyl)but-3-en-2-one (86 mg, 0.4 mmol), (2*S*,3*R*)-

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HyperBTM (6 mg, 20.0 μmol), and *N*,*N*-diisopropylethylamine (71 μL, 0.4 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (50 mg, 46%) as a colorless oil; $[\alpha]_D^{20}$ −92.3 (*c*, 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 9.6 min, t_R (major): 11.0 min, 98:2 er; IR ν_{max} (film) 1850 (C=O), 1165 (C−O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.49−7.47 (1H, m, Ar*H*), 7.48 (1H, d, *J* 16.0, ArC*H*=CH), 7.28 (1H, d, *J* 16.0, ArC*H*=CH), 7.29−7.22 (3H, m, Ar*H*), 6.09 (1H, d, *J* 16.0, ArCH=C*H*), 4.11 (1H, q, *J* 7.8, C(3)*H*), 2.41 (3H, s, ArCH_3), 1.38 (3H, d, *J* 7.8, C(3)CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −79.7 (CF_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C 168.1 (*C*(2)), 136.4 (Ar*C*(1)), 135.7 (ArCH=CH), 134.0 (Ar*C*(2)), 130.7 (Ar*C*(4)H), 129.2 (Ar*C*(3)H), 126.3 (Ar*C*(6)H), 125.9 (ArCH=CH), 123.5 (q, *J* 281.3, *C*F_3), 116.5 (Ar*C*(5)H), 78.3 (q, *J* 33.0, *C*(4)), 51.9 (*C*(3)), 19.8 (ArCH_3), 9.8 (CCH_3). HRMS (ESI+) *m*/*z* [M + OH]$^-$ calcd for $C_{14}H_{14}F_3O_3$ 287.0901, found 287.0903.

(3S,4R)-3-Ethyl-4-((E)-styryl)-4-(trifluoromethyl)oxetan-2-one ***(27)***. Following General Procedure D, 2-(trimethylsilyl)butanoic acid (64 mg, 0.4 mmol), *N*,*N*-diisopropylethylamine (105 μL, 0.6 mmol), pivaloyl chloride (66 μL, 0.6 mmol), and MTBE (2 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one (40 mg, 0.2 mmol), (2*S*,3*R*)-HyperBTM (3 mg, 10.0 μmol), and *N*,*N*-diisopropylethylamine (35 μL, 0.2 mmol) for 18 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 10 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 94:6 30 CV)], the title compound (36 mg, 67%) as a colorless oil; $[\alpha]_D^{20}$ −135.6 (*c*, 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 4.7 min, t_R (major): 5.4 min, 99:1 er; IR ν_{max} (film) 1846 (C=O), 1161 (C−O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.49−7.36 (5H, m, Ar*H*), 7.06 (1H, d, *J* 16.0, CH=C*H*Ph), 6.24 (1H, d, *J* 16.0, C*H*=CHPh), 3.89 (1H, dd, *J* 8.8, 7.9, C(3)*H*), 1.90−1.81 (1H, m, C(3)CH_AH_B), 1.79−1.70 (1H, m, C(3)CH_AH_B), 1.09 (3H, t, *J* 7.5, C(3)CH_2CH_3). ^{19}F NMR (471 MHz, $CDCl_3$) δ_F −79.8 (m, CF_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C 167.5 (*C*O), 137.5 (ArCH=CH), 134.6 (Ph*C*(1)), 129.3 (Ph*C*(4)H), 128.9 (Ph*C*(3,5)H), 128.0 (ArCH=CH), 127.1 (Ph*C*(2,6)H), 123.4 (q, *J* 282.1, *C*F_3), 114.9 (ArCH=CH), 78.3 (q, *J* 33.3, *C*CF_3), 58.8 (*C*(3)), 18.7 (CH_2CH_3), 11.5 (CH_2CH_3). HRMS (ESI+) *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}F_3O_2$ 271.0940, found 271.0941.

(3S,4R)-3-Allyl-4-((E)-styryl)-4-(trifluoromethyl)oxetan-2-one ***(28)***. Following General Procedure D, 2-(trimethylsilyl)pent-4-enoic acid (69 mg, 0.4 mmol), *N*,*N*-diisopropylethylamine (105 μL, 0.6 mmol), pivaloyl chloride (66 μL, 0.6 mmol), and MTBE (2 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one (40 mg, 0.2 mmol), (2*S*, 3*R*)-HyperBTM (3 mg, 10.0 μmol), and *N*,*N*-diisopropylethylamine (35 μL, 0.2 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 10 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 94:6 30 CV)], the title compound (34 mg, 60%) as a white solid; mp 54−56 °C; $[\alpha]_D^{20}$ −111.2 (*c*, 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (99.8:0.2 hexane:IPA, flow rate 0.5 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 21.6 min, t_R (major): 25.3 min, >99:1 er; IR ν_{max} (film) 1856 (C=O), 1163 (C−O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.48−7.38 (5H, m, Ar*H*), 7.05 (1H, d, *J* 16.0, CH=C*H*Ph), 6.24 (1H, d, *J* 16.1, C*H*=CHPh), 5.85−5.72 (1H, m, C*H*=CH_2), 5.24−5.15 (2H, m, CH=CH_2), 4.10 (1H, dd, *J* 10.1, 6.4, C(3)*H*), 2.66−2.43 (2H, m, C(3)CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ_F −79.6 (s, CF_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C 166.8 (*C*O), 137.4 (PhCH=CH), 134.5 (Ph*C*(1)), 132.4 (Ph*C*(4)H), 129.3 (CH=CH_2), 128.9 (Ph*C*(3,5)H), 127.1 (Ph*C*(2,6)H), 123.3 (q, *J* 281.8, *C*F_3), 118.4 (CH=CH_2), 114.9 (PhCH=CH), 78.3 (q, *J* 33.2, *C*CF_3), 56.3 (*C*(3)), 29.0 (*C*(3)CH_2). HRMS (ESI+) *m*/*z* [M + OH]$^-$ calcd for $C_{15}H_{14}F_3O_3$ 299.0901, found 299.0899.

(3S,4R)-3-(Prop-2-yn-1-yl)-4-((E)-styryl)-4-(trifluoromethyl)-oxetan-2-one ***(29)***. Following General Procedure D, 2-(trimethylsilyl)pent-4-ynoic acid (68 mg, 0.4 mmol), *N*,*N*-diisopropylethylamine (105 μL, 0.6 mmol), pivaloyl chloride (66 μL, 0.6 mmol), and MTBE (2 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one (40 mg, 0.2 mmol), (2*S*, 3*R*)-HyperBTM (3 mg, 10.0 μmol), and *N*,*N*-diisopropylethylamine (35 μL, 0.2 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 10 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 94:6 30 CV)], the title compound (31 mg, 55%) as a colorless solid; mp 36−38 °C; $[\alpha]_D^{20}$ +19.4 (*c*, 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 7.4 min, t_R (major): 10.0 min, 98:2 er; IR ν_{max} (film) 3300 (C≡C), 1856 (C=O), 1161 (C−O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.52−7.37 (5H, m, Ar*H*), 7.09 (1H, d, *J* 16.0, CH=C*H*Ph), 6.42 (1H, d, *J* 16.1, C*H*=CHPh), 4.22 (1H, dd, *J* 11.2, 5.2, C≡C*H*), 2.78−2.55 (2H, m, C(3)CH_2), 2.18 (1H, t, *J* 2.7, C(3)*H*). ^{19}F NMR (282 MHz, $CDCl_3$) δ_F −79.7 (s, CF_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C 165.2 (*C*O), 137.9 (PhCH=CH), 134.5 (Ph*C*(1)), 129.5 (Ph*C*(4)H), 128.9 (Ph*C*(3,5)H), 127.2 (Ph*C*(2,6)-H), 123.5 (q, *J* 282.6, *C*F_3), 114.3 (PhCH=CH), 78.3 (q, *J* 33.2, *C*CF_3), 71.6 (C≡CH), 56.0 (C≡CH, C(3)), 15.1 (C(3)CH_2). HRMS (ESI+) *m*/*z* [M + OH]$^-$ calcd for $C_{15}H_{12}F_3O_3$ 297.0744, found 297.0743.

(3S,4R)-3-Benzyl-4-((E)-styryl)-4-(trifluoromethyl)oxetan-2-one ***(30)***. Following General Procedure D, 3-phenyl-2-(trimethylsilyl)-propanoic acid (112 mg, 0.5 mmol), *N*,*N*-diisopropylethylamine (132 μL, 0.75 mmol), pivaloyl chloride (92 μL, 0.75 mmol), and MTBE (3 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one (50 mg, 0.25 mmol), (2*S*,3*R*)-HyperBTM (4 mg, 12.5 μmol), and *N*,*N*-diisopropylethylamine (44 μL, 0.25 mmol) for 20 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 95:5 40 CV)], the title compound (42 mg, 58%) as a colorless oil; $[\alpha]_D^{20}$ +25.9 (*c* 0.8, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (99.5:0.5 hexane:IPA, flow rate 0.7 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 16.7 min, t_R (major):22.4 min, 99:1 er; IR ν_{max} (film) 1854 (C=O), 1161 (C−O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.48−7.18 (10H, m, Ph*H*), 7.08 (1H, d, *J* 16.0, CH=C*H*Ph), 6.05 (1H, d, *J* 16.0, C*H*=CHPh), 4.39 (1H, dd, *J* 10.0, 6.8, C(3)*H*), 3.23 (1H, dd, *J* 15.0, 6.7, C(3)H_AH_B), 2.98 (1H, dd, *J* 15.0, 10.0, C(3)CH_AH_B). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −79.6 (CF_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C 163.6 (*C*(2)), 137.1 (CH=CHPh), 135.8 (CH=CHPh*C*(1)), 134.4 (CH=CHPh*C*(1)), 129.4 (CH=CHPh*C*(4)H), 129.0 (C(3)-CH_2Ph*C*(3,5)H), CH=CHPh*C*(2,6)H), 128.4 (CH=CHPh*C*(3,5)-H), 127.4 (C(3)CH_2Ph*C*(4)H), 127.2 (C(3)CH_2Ph*C*(2,6)H), 123.2 (q, *J* 283.1, *C*F_3), 115.1 (CH=CHPh), 78.6 (q, *J* 33.5, *C*(4)), 57.9 (*C*(3)H), 30.9 (*C*(3)CH_2). HRMS (ESI+) *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{15}F_3NaO_2$ 355.0916, found 355.0922.

(3S,4R)-3-(Naphthalen-2-ylmethyl)-4-((E)-styryl)-4-(trifluoromethyl)oxetan-2-one ***(31)***. Following General Procedure D, 3-(naphthalen-2-yl)-2-(trimethylsilyl)propanoic acid (114 mg, 0.4 mmol), *N*,*N*-diisopropylethylamine (105 μL, 0.6 mmol), pivaloyl chloride (66 μL, 0.6 mmol), and MTBE (2 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one (40 mg, 0.2 mmol), (2*S*, 3*R*)-HyperBTM (3 mg, 10.0 μmol), and *N*,*N*-diisopropylethylamine (35 μL, 0.2 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 10 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 94:6 30 CV)], the title compound (50 mg, 52%) as a colorless oil; $[\alpha]_D^{20}$ +107.5 (*c*, 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 19.4 min, t_R (major): 34.5 min, 95:5 er; IR ν_{max} (film) 1852 (C=O), 1163 (C−O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.88−7.86 (2H, m, Ar*C*H), 7.79−7.78 (1H, m, Ar*C*H), 7.62 (1H, s, Ar*H*), 7.55−7.51 (2H, m, Ar*C*H), 7.45−7.40 (5H, m, Ar*C*H), 7.33−7.31 (1H, m, CH=CHPh(4)*H*), 7.11 (1H, d, *J* 16.0, CH=C*H*Ph), 6.05 (1H, d, *J* 16.0, C*H*=CHPh), 4.51 (1H, dd, *J* 10.5, 6.6, C(3)*H*), 3.40 (1H, dd, *J* 15.0, 6.4, C(3)CH_AH_B), 3.16 (1H, dd, *J* 15.0, 10.4, C(3)CH_AH_B). ^{19}F NMR (282 MHz, $CDCl_3$) δ_F −79.6 (s, CF_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C 166.8 (*C*O), 137.1 (ArCH=CH), 134.4 (Ar*C*(2)), 133.4 (Ph*C*(1)), 133.1 (Ar*C*(8a)), 132.6 (Ar*C*(4a)), 129.4 (Ar*C*(1)-H), 129.0 (Ph*C*(3,5)H), 128.9 (Ar*C*(3)H), 127.8 (Ar*C*(8)H), 127.6 (Ph*C*(4)H), 127.25 (Ar*C*(4)H), 127.20 (Ph*C*(2,6)H), 126.6 (Ar*C*(5)H), 126.1 (Ar*C*(6,7)H), 123.3 (q, *J* 281.8, *C*F_3), 115.2

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(ArCH═CH), 78.7 (q, *J* 33.2, CCF_3), 57.8 (C(3)), 31.2 (CH_2Ar). HRMS (ESI+) *m/z* [M + Na]$^+$ calcd for $C_{23}H_{17}F_3NaO_2$ 405.1073, found 405.1067.

(3S,4S)-3-Methyl-4-((E)-1-phenylprop-1-en-2-yl)-4-(trifluoromethyl)oxetan-2-one ***(32)***. Following General Procedure D, 2-(trimethylsilyl)propanoic acid (117 mg, 0.8 mmol), *N,N*-diisopropylethylamine (210 μL, 1.2 mmol), pivaloyl chloride (132 μL, 1.2 mmol), and MTBE (4.5 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-3-methyl-4-phenylbut-3-en-2-one (86 mg, 0.4 mmol), (2*S*,3*R*)-HyperBTM (6 mg, 20.0 μmol), and *N,N*-diisopropylethylamine (71 μL, 0.4 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 96:4 40 CV)], the title compound (63 mg, 58%) as a colorless oil; $[\alpha]_D^{20}$ +32.3 (*c*, 1.1, $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (99.8:0.2 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 13.1 min, t_R (major): 17.4 min, >99:1 er; IR ν_{max} (film) 1846 (C═O), 1171 (C−O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.44−7.40 (2H, m, PhC(3,5)*H*), 7.36−7.32 (3H, m, PHC(2,4,6)*H*), 6.94 (1H, s, ArC*H*), 4.07 (1H, q, *J* 7.8, C(3)*H*), 2.00 (3H, t, *J* 1.4, CCH_3), 1.41 (3H, d, *J* 7.7, C(3)H_AH_B). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −76.5 (CF_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C 168.3 (*C*(2)), 135.5 (PhCH═*C*), 132.6 (PhC*H*═C), 129.2 (PhC(3,5)H), 128.4 (PhC(2,6)H), 127.8 (PhC(4)H), 125.4 (PHC(1)), 123.8 (q, *J* 283.6, CF_3), 80.7 (t, *J* 31.6, *C*(4)), 51.5 (*C*(3)), 15.2 (C(3)CH_3), 9.7 (CCH_3). HRMS (ESI+) *m/z* [M + H]$^+$ calcd for $C_{14}H_{14}F_3O_2$ 271.0940, found 271.0936.

(3S,4S)-4-((E)-1-(4-Bromophenyl)prop-1-en-2-yl)-3-methyl-4-(trifluoromethyl)oxetan-2-one ***(33)***. Following General Procedure D, 2-(trimethylsilyl)propanoic acid (117 mg, 0.8 mmol), *N,N*-diisopropylethylamine (210 μL, 1.2 mmol), pivaloyl chloride (132 μL, 1.2 mmol), and MTBE (4.5 mL) for 15 min, followed by (*E*)-4-(4-bromophenyl)-1,1,1-trifluoro-3-methylbut-3-en-2-one (117 mg, 0.4 mmol), (2*S*,3*R*)-HyperBTM (6 mg, 20.0 μmol), and *N,N*-diisopropylethylamine (71 μL, 0.4 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (112 mg, 80%) as a white solid; mp 38−40 °C; $[\alpha]_D^{20}$ −2.1 (*c*, 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 24.6 min, t_R (major): 39.4 min, >99:1 er; IR ν_{max} (film) 1848 (C═O), 1173 (C−O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.56−7.53 (2H, m, ArC(3,5)*H*), 7.23−7.20 (2H, m, ArC(2,6)*H*), 6.87 (1H, s, C═C*H*), 4.07 (1H, q, *J* 7.7, C(3)*H*), 1.97 (3H, s, CH═CCH_3), 1.40 (3H, d, *J* 7.7, C(3)CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −76.4 (CF_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C 168.0 (*C*(2)), 134.3 (ArCH═*C*), 131.6 (ArC(3,5)H), 131.5 (ArCH═C), 130.8 (ArC(2,6)H), 126.4 (Ar*C*(4)), 123.7 (q, *J* 282.5, CF_3), 121.9 (ArC(1)), 80.7 (q, *J* 31.3, *C*(4)), 51.5 (*C*(3)), 15.2 (C(3)CH_3), 9.7 (CCH_3). HRMS (ESI+) *m/z* [M + OH]$^-$ calcd for $C_{14}H_{13}BrF_3O_3$ 365.0006, found 365.0010.

(3S,4S)-4-((E)-1-(4-Methoxyphenyl)prop-1-en-2-yl)-3-methyl-4-(trifluoromethyl)oxetan-2-one ***(34)***. Following General Procedure D, 2-(trimethylsilyl)propanoic acid (117 mg, 0.8 mmol), *N,N*-diisopropylethylamine (210 μL, 1.2 mmol), pivaloyl chloride (132 μL, 1.2 mmol), and MTBE (4.5 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-(4-methoxyphenyl)-3-methylbut-3-en-2-one (98 mg, 0.4 mmol), (2*S*,3*R*)-HyperBTM (6 mg, 20.0 μmol), and *N,N*-diisopropylethylamine (71 μL, 0.4 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 92:8 40 CV)], the title compound (46 mg, 38%) as a white solid; mp 62−64 °C; $[\alpha]_D^{20}$ +13.6 (*c*, 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralpak AS-H (99.5:0.5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 6.0 min, t_R (major): 7.8 min, 99:1 er; IR ν_{max} (film) 1844 (C═O), 1169 (C−O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.33−7.30 (2H, m, ArC(2,6)*H*), 6.96−6.93 (2H, m, ArC(3,5)*H*), 6.85 (1H, s, C═C*H*), 4.05 (1H, q, *J* 7.7, C(3)*H*), 3.86 (3H, s, OCH_3), 2.00 (3H, t, *J* 1.5, CH═CCH_3), 1.39 (3H, d, *J* 7.7, C(3)CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −76.6 (CF_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C 168.4 (*C*(2)), 159.1 (Ar*C*(4)), 132.0 (ArCH═C), 130.7 (Ar*C*(2,6)H), 128.0 (ArCH═*C*), 123.9 (q, *J* 283.9, CF_3), 123.3 (Ar*C*(1)), 113.8 (Ar*C*(3,5)H), 80.9 (q, *J* 31.6, *C*(4)), 55.3 (OCH_3), 51.5 (*C*(3)), 15.3 (C(3)CH_3), 9.8 (CCH_3). HRMS (ESI+) *m/z* [M + H]$^+$ calcd for $C_{15}H_{16}F_3O_3$ 301.1046, found 301.1042.

(3S,4S)-4-((E)-1-(Furan-2-yl)prop-1-en-2-yl)-3-methyl-4-(trifluoromethyl)oxetan-2-one ***(35)***. Following General Procedure D, 2-(trimethylsilyl)propanoic acid (117 mg, 0.8 mmol), *N,N*-diisopropylethylamine (210 μL, 1.2 mmol), pivaloyl chloride (132 μL, 1.2 mmol), and MTBE (4.5 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-4-(furan-2-yl)-3-methylbut-3-en-2-one (81 mg, 0.4 mmol), (2*S*,3*R*)-HyperBTM (6 mg, 20.0 μmol), and *N,N*-diisopropylethylamine (71 μL, 0.4 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 25 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 96:4 40 CV)], the title compound (56 mg, 54%) as a yellow oil; $[\alpha]_D^{20}$ +39.5 (*c*, 1.6, $CHCl_3$); Chiral HPLC analysis, Chiralpak AD-H (99.9:0.1 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (major): 6.4 min, >99:1 er; IR ν_{max} (film) 1848 (C═O), 1175 (C−O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.51 (1H, d, *J* 1.1, ArC(5)*H*), 6.70 (1H, s, ArC*H*), 6.50−6.48 (2H, m, ArC(3,4)*H*), 4.05 (1H, q, *J* 7.8, C(3)*H*), 2.14 (3H, s, CCH_3), 1.39 (3H, d, *J* 7.6, C(3)CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −76.5 (CF_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C 168.1 (*C*(2)), 151.4 (Ar*C*(2)), 142.9 (Ar*C*(5)H), 123.7 (q, *J* 283.8, CF_3), 122.5 (ArCH═*C*), 120.4 (Ar*C*(4)H), 112.3 (ArCH═C), 111.6 (Ar*C*(3)H), 80.8 (q, *J* 31.8, *C*(4)), 51.5 (*C*(3)), 15.5 (C(3)CH_3), 9.8 (CCH_3). HRMS (ESI+) *m/z* [M + H]$^+$ calcd for $C_{12}H_{12}F_3O_3$ 261.0733, found 261.0730.

(3S,4S)-3-Ethyl-4-((E)-1-phenylprop-1-en-2-yl)-4-(trifluoromethyl)oxetan-2-one ***(36)***. Following General Procedure D, 2-(trimethylsilyl)butanoic acid (64 mg, 0.4 mmol), *N,N*-diisopropylethylamine (105 μL, 0.6 mmol), pivaloyl chloride (66 μL, 0.6 mmol), and MTBE (2 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-3-methyl-4-phenylbut-3-en-2-one (40 mg, 0.2 mmol), (2*S*,3*R*)-HyperBTM (3 mg, 10.0 μmol), and *N,N*-diisopropylethylamine (35 μL, 0.2 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 10 g, 36 mL min^{-1}, petrol:Et_2O (99:1 4 CV, 99:1 to 94:6 20 CV)], the title compound (42 mg, 72%) as a mixture of diastereoisomers in the ratio of 75:25, colorless oil; $[\alpha]_D^{20}$ −28.7 (*c*, 0.4, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (99.9:0.1 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), major diastereoisomer: t_R (major): 7.0 min, t_R (minor): 7.4 min, 97:3 er; minor diastereoisomer: t_R(major): 13.9 min, t_R(minor): 20.2 min,90:10 er; IR ν_{max} (film) 1850 (C═O), 1151(C−O); ^{1}H NMR (500 MHz, $CDCl_3$) major diastereoisomer: δ_H 7.43−7.40 (2H, m, Ph*H*), 7.34−7.32 (3H, m, Ph*H*), 6.93 (1H, s, C*H*Ph), 3.89 (1H, dd, *J* 9.6, 7.2, C(3)*H*), 2.01 (3H, m, CH═CCH_2), 1.93−1.79 (2H, m, CH_2CH_3), 1.18 (3H, t, *J* 7.5, CH_2CH_3); minor diastereoisomer: δ_H 7.43−7.40 (2H, m, Ph*H*), 7.34−7.32 (3H, m, Ph*H*), 6.84 (1H, s, C*H*Ph), 3.70 (1H, dd, *J* 9.6, 7.2, C(3)*H*), 2.04−2.03 (3H, m, CH═CCH_2), 1.93−1.79 (2H, m, CH_2CH_3), 1.22 (3H, t, *J* 7.5, CH_2CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) major diastereoisomer: δ_F −72.5 (s, CF_3); minor diastereoisomer: δ_F −76.5 (s, CF_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) major diastereoisomer: δ_C 167.7 (CO), 135.6 (Ph*C*(1)), 132.2 (CH═C), 129.2 (Ph*C*(3,5)H), 128.4 (Ph*C*(2,6)H), 127.7 (PhC(4)H), 125.8 (PhCH═CCH_3), 123.8 (q, *J* 283.2, CF_3), 80.4 (q, *J* 31.5, CCF_3), 71.9 (C≡CH), 57.9 (C(3)), 26.5 (CCH_3), 18.9 (CH_2CH_3), 11.3 (CH_2CH_3); minor diastereoisomer: δ_C 167.9 (CO), 135.4 (Ph*C*(1)), 131.4 (ArCH), 129.1 (Ph*C*(3,5)H), 128.4 (Ph*C*(2,6)H), 127.8 (PhC(4)H), 125.8 (PhCH═CCH_3), 123.6 (q, *J* 283.2, CF_3), 62.0 (C(3)), 23.2 (CCH_3), 15.1 (CH_2CH_3), 10.1 (CH_2CH_3). HRMS (ESI+) *m/z* [M + H]$^+$ calcd for $C_{15}H_{16}F_3O_2$ 285.1097, found 285.1099.

(3S,4S)-3-Allyl-4-((E)-1-phenylprop-1-en-2-yl)-4-(trifluoromethyl)oxetan-2-one ***(37)***. Following General Procedure D, 2-(trimethylsilyl)pent-4-enoic acid (69 mg, 0.4 mmol), *N,N*-diisopropylethylamine (105 μL, 0.6 mmol), pivaloyl chloride (66 μL, 0.6 mmol), and MTBE (3 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-3-methyl-4-phenylbut-3-en-2-one (43 mg, 0.2 mmol), (2*S*,3*R*)-HyperBTM (3 mg, 10.0 μmol), and *N,N*-diisopropylethylamine (35 μL, 0.2 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 10 g, 36 mL min^{-1}, petrol:Et_2O (99:1 4 CV, 99:1 to 95:5 30 CV)], the title compound (42 mg, 70%) as a mixture

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of diastereoisomers in the ratio of 75:25, colorless oil; $[\alpha]_D^{20}$ −23.5 (*c*, 0.4, $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (99.8:0.2 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), major diastereoisomer: t_R (minor): 10.2 min, t_R (major): 13.1 min, 99:1 er; minor diastereoisomer: t_R (major): 16.6 min, t_R (minor): 19.1 min,93:7 er; IR ν_{max} (film) 1854 (C═O), 1173 (C−O), 937 (C═C); ^{1}H NMR (400 MHz, $CDCl_3$) major diastereoisomer: δ_H 7.44−7.32 (5H, m, Ar*H*), 6.95 (1H, s, C*H*Ph), 5.93−5.84 (1H, m, C*H*═CH_2), 5.24−5.19 (2H, m, CH═CH_2), 4.07 (1H, t, *J* 7.8, C(3)*H*), 2.59−2.56 (2H, m, C(3)CH_2), 2.02−2.01 (3H, m, CH_3); minor diastereoisomer: δ_H 7.44−7.32 (5H, m, Ar*H*), 6.84 (1H, d, *J* 16.1, C*H*Ph), 5.93−5.84 (1H, m, C*H*═CCH_3), 5.32−5.21 (2H, m, CH═CH_2), 3.85 (1H, t, *J* 8.1, C(3)*H*), 2.88−2.70 (2H, m, C(3)CH_2), 2.03 (3H, m, CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) major diastereoisomer: δ_F −72.4 (s, CF_3); minor diastereoisomer: δ_F −76.5 (s, CF_3). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) major diastereoisomer: δ_C 167.1 (CO), 135.5 (PhC(1)), 132.6 (CH═CH_2), 132.4 (PhC(4)H), 129.2 (PhC(3,5)H), 128.4 (PhC(2,6)H), 127.8 (PhCH), 125.6 (PhCH═CCH_3), 123.8 (q, *J* 283.8, CF_3), 118.6 (CH═CH_2), 80.5 (q, *J* 32.1, CCF_3), 55.8 (C(3)), 29.1 (C(3)CH_2), 15.2 (CH_3); minor diastereoisomer: δ_C 167.2 (CO), 135.3 (PhC(1)), 132.7 (CH═CH_2), 131.7 (PhC(4)H), 129.1 (PhC(3,5)H), 128.4 (PhC(2,6)H), 127.9 (PhCH), 127.0 (PhCH═CCH_3), 123.6 (q, *J* 283.8, CF_3), 118.9 (CH═CH_2), 60.0 (C(3)), 29.4 (C(3)CH_2), 14.2 (CH_3). HRMS (ESI+) *m*/*z* [M + OH]$^-$ calcd for $C_{16}H_{16}F_3O_3$ 313.1057, found 313.1058.

(3S,4S)-4-((E)-1-Phenylprop-1-en-2-yl)-3-(prop-2-yn-1-yl)-4-(trifluoromethyl)oxetan-2-one ***(38)***. Following General Procedure D, 2-(trimethylsilyl)pent-4-ynoic acid (68 mg, 0.4 mmol), *N*,*N*-diisopropylethylamine (105 μL, 0.6 mmol), pivaloyl chloride (66 μL, 0.6 mmol), and MTBE (2 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-3-methyl-4-phenylbut-3-en-2-one (40 mg, 0.2 mmol), (2*S*,3*R*)-HyperBTM (3 mg, 10.0 μmol), and *N*,*N*-diisopropylethylamine (35 μL, 0.2 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 10 g, 36 mL min^{-1}, petrol:Et_2O (99:1 4 CV, 99:1 to 95:5 30 CV)], the title compound (36 mg, 61%) as a mixture of diastereoisomers in the ratio of 70:30, colorless oil; $[\alpha]_D^{20}$ +9.8 (*c*, 0.6, $CHCl_3$); Chiral HPLC analysis, Chiralcel OJ-H (99.8:0.2 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), major diastereoisomer: t_R (major): 26.5 min, t_R (minor): 31.3 min, 98:2 er; minor diastereoisomer: Chiralcel OD-H (99.9:0.1 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 24.8 min, t_R (major): 28.9 min,90:10 er; IR ν_{max} (film) 1855 (C═O), 1173 (C−O), 937 (C═C).

^{1}H NMR (500 MHz, $CDCl_3$) major diastereoisomer: δ_H 7.44−7.33 (5H, m, Ph*H*), 6.96 (1H, s, C*H*Ph), 4.20 (1H, dd, *J* 8.4, 5.5, C≡C*H*), 2.79−2.68 (2H, m, C(3)CH_2), 2.16 (1H, t, *J* 2.7, C(3)*H*), 2.11−2.10 (3H, m, CH_3); minor diastereoisomer: δ_H 7.44−7.33 (5H, m, Ph*H*), 6.96 (1H, s, C*H*Ph), 4.06 (1H, dd, *J* 10.1, 6.0, C≡C*H*), 3.01−2.88 (2H, m, C(3)CH_2), 2.20 (1H, t, *J* 2.7, C(2)*H*), 2.11−2.10 (3H, m, CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) major diastereoisomer: δ_F −72.5 (s, CF_3); minor diastereoisomer: δ_F −76.9 (s, CF_3). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) major diastereoisomer: δ_C 165.6 (CO), 135.4 (PhC(1)), 133.0 (ArCH), 129.2 (PhC(3,5)H), 128.5 (PhC(2,6)H), 127.9 (PhC(4)H), 125.4 (PhCH═CCH_3), 123.5 (q, *J* 283.4, CF_3), 80.5 (q, *J* 32.1, CCF_3), 71.9 (C≡CH), 58.9 (C≡CH), 55.7 (C(3)), 15.2 (C(3)CH_2), 14.2 (CH_3); minor diastereoisomer: δ_C 165.7 (CO), 135.3 (PhC(1)), 132.4 (ArCH), 129.1 (PhC(3,5)H), 128.5 (PhC(2,6)H), 128.0 (PhC(4)H), 125.2 (PhCH═CCH_3), 123.5 (q, *J* 283.4, CF_3), 71.4 (C≡CH), 58.9 (C≡CH), 55.7 (C(3)), 15.2 (C(3)CH_2), 14.0 (CH_3). HRMS (ESI+) *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{13}NaF_3O_2$ 317.0760, found 317.0757.

(3S,4S)-3-Benzyl-4-((E)-1-phenylprop-1-en-2-yl)-4-(trifluoromethyl)oxetan-2-one ***(39)***. Following General Procedure D, 3-phenyl-2-(trimethylsilyl)propanoic acid (90 mg, 0.4 mmol), *N*,*N*-diisopropylethylamine (105 μL, 0.6 mmol), pivaloyl chloride (66 μL, 0.6 mmol), and MTBE (2 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-3-methyl-4-phenylbut-3-en-2-one (40 mg, 0.2 mmol), (2*S*,3*R*)-HyperBTM (3 mg, 10.0 μmol), and *N*,*N*-diisopropylethylamine (35 μL, 0.2 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 10 g, 36 mL min^{-1}, petrol:Et_2O (99:1 4 CV, 99:1 to 94:6 20 CV)], the title compound (53 mg, 75%) as a mixture of diastereoisomers in the ratio of 76:24, white solid; mp 66−68 °C; $[\alpha]_D^{20}$ +3.3 (*c*, 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (99.9:0.1 hexane:IPA, flow rate 0.5 mL min^{-1}, 211 nm, 30 °C), major diastereoisomer: t_R (major): 83.6 min, t_R (minor): 101.5 min, >99:1 er; minor diastereoisomer: Chiralcel OD-H (99.9:0.1 hexane:IPA, flow rate 0.5 mL min^{-1}, 254 nm, 30 °C), t_R(major): 64.1 min, t_R(minor): 108.2 min,96:4 er; IR ν_{max} (film) 1850 (C═O), 1173 (C−O); ^{1}H NMR (500 MHz, $CDCl_3$) major diastereoisomer: δ_H 7.44−7.29 (7H, m, Ph*H*), 7.25−7.23 (3H, m, Ph*H*), 6.98 (1H, s, C*H*Ph), 4.34 (1H, dd, *J* 8.7, 7.5, C(3)*H*), 3.18−3.07 (2H, m, C(3)CH_2), 1.93−1.92 (3H, m, CH_3); minor diastereoisomer: 7.44−7.29 (10H, m, Ph*H*), 6.65 (1H, s, C*H*Ph), 4.07 (1H, t, *J* 7.6, C(3)*H*), 3.48−3.19 (2H, m, C(3)CH_2), 1.90 (3H, m, CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) major diastereoisomer: δ_F −72.3 (s, CF_3); minor diastereoisomer: δ_F −76.2 (s, CF_3). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) major diastereoisomer: δ_C 167.1 (C(2)), 136.7 (C(3)-CH_2PhC(1)), 135.5 (C═CHPhC(1)), 132.7 (PhCH), 129.2 (C═CHPhC(4)H), 128.9 (C═CHPhC(2,6)H), 128.48 (C(3)-CH_2PhC(3,5)H), 128.46 (C═CHPhC(3,5)H), 127.9 (C(3)-CH_2PhC(4)H), 127.4 (C(3)CH_2PhC(2,6)H), 125.6 (PhCH═CCH_3), 123.8 (q, *J* 284.0, CF_3), 79.2 (q, *J* 33.1, CCF_3), 30.9 (CH_2Ar), 57.0 (C(3)), 15.3 (CH_3); minor diastereoisomer: δ_C 167.2 (C(2)), 135.7 (C(3)CH_2PhC(1)), 135.2 (C═CHPhC(1)), 131.8 (PhCH), 129.1 (C═CHPhC(4)), 129.0 (C═CHPhC(2,6)H), 128.8 (C(3)CH_2PhC(3,5)H), 128.4 (C═CHPhC(3,5)H), 127.9 (C(3)-CH_2PhC(4)), 127.4 (C(3)CH_2PhC(2,6)H), 125.6 (PhCH═CCH_3), 123.8 (q, *J* 284.0, CF_3), 61.9 (C(3)), 31.1 (CH_2Ar), 14.1 (CH_3). HRMS (ESI+) *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{17}NaF_3O_2$ 369.1073, found 369.1072.

(3S,4S)-3-(Naphthalen-2-ylmethyl)-4-((E)-1-phenylprop-1-en-2-yl)-4-(trifluoromethyl)oxetan-2-one ***(40)***. Following General Procedure D, 3-(naphthalen-2-yl)-2-(trimethylsilyl)propanoic acid (114 mg, 0.4 mmol), *N*,*N*-diisopropylethylamine (105 μL, 0.6 mmol), pivaloyl chloride (66 μL, 0.6 mmol), and MTBE (2 mL) for 15 min, followed by (*E*)-1,1,1-trifluoro-3-methyl-4-phenylbut-3-en-2-one (40 mg, 0.2 mmol), (2*S*,3*R*)-HyperBTM (3 mg, 10.0 μmol), and *N*,*N*-diisopropylethylamine (35 μL, 0.2 mmol) for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 10 g, 36 mL min^{-1}, petrol:Et_2O (99:1 4 CV, 99:1 to 95:5 30 CV)], the title compound (63 mg, 78%) as a mixture of diastereoisomers in the ratio of 70:30, white solid; mp 68−70 °C; $[\alpha]_D^{20}$ +8.0 (*c*, 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), major diastereoisomer: t_R (major): 17.2 min, t_R (minor): 47.7 min, >99:1 er; minor diastereoisomer: t_R (major): 10.5 min, t_R (minor): 13.1 min, 97:3 er; IR ν_{max} (film) 1850 (C═O), 1173 (C−O), 934 (C═C); ^{1}H NMR (500 MHz, $CDCl_3$) major diastereoisomer: δ_H 7.87−7.79 (3H, m, Ar*H*), 7.70 (1H, s, Ar*H*), 7.51−7.49 (2H, m, Ar*H*), 7.45−7.42 (2H, m, Ar*H*), 7.38−7.34 (3H, m, Ar*H*), 7.22−7.20 (1H, m, Ar*H*), 7.01 (1H, s, C*H*Ph), 4.46 (1H, dd, *J* 8.4, 7.6, C(3)*H*), 3.30 (2H, qd, *J* 15.0, 8.4, C(3)CH_2), 1.95 (3H, m, CH_3); minor diastereoisomer: (Selected signal)δ_H 6.70 (1H, s, C*H*Ph), 4.19 (1H, t, *J* 7.6, C(3)*H*), 3.64−3.37 (2H, m, C(3)CH_2), 1.90 (3H, m, CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) major diastereoisomer: δ_F −72.2 (s, CF_3); minor diastereoisomer: δ_F −76.1 (s, CF_3). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) major diastereoisomer: δ_C 167.1 (CO), 135.5 (ArC(2)), 133.4 (PhC(1)), 133.2 (ArC(8a)), 132.8 (ArC(1)H), 132.5 (ArC(4a)), 129.3 (PhC(3,5)H), 128.5 (ArC(3)H), 127.9 (ArC(8)H), 127.7 (PhC(4)-H), 127.6 (PhC(2,6)H), 127.2 (ArC(4)H), 126.5 (ArC(5)H), 126.4 (ArC(6,7)H), 126.1 (ArCH═CCH_3), 125.6 (ArCH═CCH_3), 123.9 (q, *J* 283.8, CF_3), 80.8 (q, *J* 31.8, CCF_3), 57.0 (C(3)), 31.1 (CH_2Ar), 15.3 (CH_3); minor diastereoisomer: δ_C 167.2 (CO), 135.2 (ArC(2)), 134.0 (PhC(1)), 133.5 (ArC(8a)), 132.5 (ArC(4a)), 131.8 (ArC(1)-H), 129.1 (PhC(3,5)H), 128.8 (ArC(3)H), 128.4 (ArC(8)H), 127.8 (PhC(4)H), 127.7 (PhC(2,6)H), 127.6 (ArC(4)H), 126.6 (ArC(5)-H), 126.5 (ArC(6,7)H), 126.1 (ArCH═CCH_3), 125.6 (ArCH═CCH_3), 123.8 (q, *J* 283.8, CF_3), 61.7 (C(3)), 31.3 (CH_2Ar), 14.2

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(CH_3). HRMS (ESI+) m/z [M + Na]$^+$ calcd for $C_{24}H_{19}NaF_3O_2$ 419.1229, found 419.1219.

(2S,3R,E)-N-Benzyl-5-(4-bromophenyl)-3-hydroxy-2-methyl-3-(trifluoromethyl)pent-4-enamide ***(43)***. β-Lactone **18** (47 mg, 0.14 mmol) and benzylamine (75 μL, 0.70 mmol) in dichloromethane (3.0 mL) at r.t. for 16 h gave, after purification by Biotage Isolera 4 [SNAP KP-Sil 10 g, 36 mL min^{-1}, CH_2Cl_2:MeOH (100:0 to 95:5, 30 CV)], the title compound (58 mg, 93%) as a white solid; mp 128−130 °C; $[\alpha]_D^{20}$ −47.3 (c, 0.4, $CHCl_3$); Chiral HPLC analysis, Chiralcel OD-H (95:5 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 46.9 min, t_R (major): 51.7 min, >99:1 er; IR ν_{max} (film) 3298 (OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.50−7.29 (9H, m, ArH), 7.03 (1H, d, J 15.6, CH═CHPh), 6.54 (1H, s, OH), 6.03 (1H, t, J 5.6, NH), 5.92 (1H, d, J 15.8, CH═CHPh), 4.50 (2H, m, NHCH_2), 2.57 (1H, d, J 7.0, C(2)H), 1.28 (3H, d, J 7.2, C(2)CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ_F −78.4 (s, CF_3). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C 175.4 (CO), 137.0 (PhC(1)), 134.7 (ArC(1)), 133.2 (ArCH═CH), 131.8 (ArC(3,5)H), 129.0 (ArC(2,6)H), 128.4 (PhC(3,5)H), 128.0 (ArCH═CH), 127.9 (PhC(2,6)H), 125.5 (q, J 286.9, CF_3), 123.2 (PhC(4)H), 122.2 (ArC(4)Br), 77.7 (q, J 27.6, CCF_3), 43.8 (NCH_2), 40.7 (C(2)), 14.0 (CCH_3). HRMS (ESI+) m/z [M + Na]$^+$ calcd for $C_{20}H_{19}NNaBrF_3O_2$ 464.0443, found 464.0437.

(S,E)-5-(4-Bromophenyl)-4-methyl-3-(trifluoromethyl)pent-4-ene-1,3-diol ***(44)***. 1 M i-Bu_2AlH (DIBAL) 1 M solution in hexane (1.74 mL, 2 equiv) was added dropwise to a solution of a β-lactone (**11**) (292 mg, 0.87 mmol) (1 equiv) in CH_2Cl_2 (0.1 M) at −78 °C under an inert atmosphere, and the reaction was allowed to stir for 90 min. Aqueous NH_4Cl was added and the mixture was allowed to warm to r.t. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give a residue, which after purification by Biotage Isolera 4 [SNAP KP-Sil 10 g, 36 mL min^{-1}, petrol:Et_2O (90:10 4 CV, 90:10 to 50:50 30 CV)] gave the title compound (161 mg, 55%) as a white solid; mp 42−44 °C; $[\alpha]_D^{20}$ −37.5 (c, 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralpak AS-H (98:2 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 14.1 min, t_R (major): 17.0 min, 95:5 er; IR ν_{max} (film) 3362(OH), 1171 (C−O); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.52−7.48 (2H, m, ArC(3,5)H), 7.18−7.16 (2H, m, ArC(2,6)H), 7.01 (1H, s, CHAr), 4.61 (1H, s, COH), 4.07−3.92 (2H, m, CH_2OH), 2.34−2.17 (2H, m, CCH_2), 1.99 (1H, s, CH_2OH), 1.90 (3H, t, J 1.2, CH_3). ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −78.2 (s, CF_3). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C 136.2 (ArC(1)), 134.4 (ArCH═CCH_3), 131.3 (ArC(3,5)H), 130.8 (ArC(2,6)H), 129.1 (ArCH═CCH_3), 125.2 (q, J 286.2, CF_3), 120.8 (ArC(4)), 79.3 (q, J 27.2, CCF_3), 59.6 (CH_2OH), 33.3 (CCH_2), 14.7 (CH_3). HRMS (ESI+) m/z [M + Na]$^+$ calcd for $C_{13}H_{14}NaBrF_3O_2$ 361.0021, found 361.0019.

(S,E)-2-(1-(4-Bromophenyl)prop-1-en-2-yl)-2-(trifluoromethyl)-oxetane ***(45)***. NaH 60% in mineral oil (24 mg, 0.6 mmol, 2 equiv) was added to a solution of a diol **44** (102 mg, 0.3 mmol, 1 equiv) in THF (0.02 M) under an inert atmosphere and the mixture was stirred at r.t. for 10 min. 2,4,6-Triisopropylbenzenesulfonyl chloride (82 mg, 0.27 mmol, 0.9 equiv) was added, and the mixture stirred for 16 h. Aqueous NH_4Cl was added and the aqueous phase extracted with EtOAc (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give a residue, which after purification by Biotage Isolera 4 [SNAP KP-Sil 10 g, 36 mL min^{-1}, petrol:Et_2O (98:2 4 CV, 98:2 to 80:20 20 CV)] gave the title compound (81 mg, 84%) as a colorless oil; $[\alpha]_D^{20}$ −15.4 (c, 0.4, $CHCl_3$); Chiral HPLC analysis, Chiralpak AD-H (99:0.2 hexane:IPA, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R (minor): 5.7 min, t_R (major): 6.0 min, 96:4 er; IR ν_{max} (film) 1157(OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.53−7.50 (2H, m, ArC(3,5)H), 7.23−7.21 (2H, m, ArC(2,6)H), 6.74 (1H, s, CHAr), 4.80−4.75 (1H, m, CH_AH_BOH), 4.58−4.53 (1H, m, C$H_A$$H_B$OH), 3.07−3.00 (1H, m, CCH_AH_B), 2.82−2.75 (1H, m, CC$H_A$$H_B$), 1.89 (3H, t, J 1.2, CH_3). ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −81.5 (s, CF_3). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C 135.4 (ArC(1)), 134.0 (ArCH═CCH_3), 131.4 (ArC(3,5)-H), 130.7 (ArC(2,6)H), 127.7 (ArCH═CCH_3), 124.9 (q, J 284.6, CF_3), 121.1 (ArC(4)), 86.2 (q, J 30.4, CCF_3), 66.7 (CH_2OH), 27.6 (CCH_2), 12.9 (CH_3). HRMS (ESI+) m/z [M + H]$^+$ calcd for $C_{13}H_{13}BrF_3O$ 321.0096, found 321.0096.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article, in its Supporting Information, and openly available in the St Andrews PURE repository that can be accessed at DOI: 10.17630/ec54103f-32b7-422b-8e9a-f2c1f623065c.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c02688.

Full experimental procedures, characterization data, NMR spectra, and HPLC chromatograms for all new compounds, as well as crystallographic data for **17**, **18**, and **34** (PDF)

Accession Codes

CCDC 2217572−2217574 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Gelbin, M. E.; Kohn, J. Synthesis and Polymerization of *N-Z*-L-Serine-β-Lactone and Serine Hydroxybenzotriazole Active Esters. *J. Am. Chem. Soc.* **1992**, *114*, 3962. (b) Machrouhi, F.; Namy, J.-L. A New Coupling Reaction Between β-Lactones and Electrophiles Mediated by a SmI_2/(NiI_2 catalytic)System. *Tetrahedron.* **1998**, *54*, 11111. (c) Romo, D.; Wang, Y.; Tennyson, R. L. β-Lactones:

Intermediates for Natural Product Total Synthesis and New Transformations. *Heterocycles* **2004**, *64*, 605. (d) Green, M. E.; Rech, J. C.; Floreancig, P. E. Total Synthesis of Theopederin D. *Angew. Chem., Int. Ed.* **2008**, *47*, 7317. (e) Chandra, B.; Fu, D.; Nelson, S. G. Catalytic Asymmetric Synthesis of Complex Polypropionates: Lewis Base Catalyzed Aldol Equivalents in the Synthesis of Erythronolide B. *Angew. Chem., Int. Ed.* **2010**, *49*, 2591. (f) Böttcher, T.; Pitscheider, M.; Sieber, S. A. Natural Products and Their Biological Targets:Proteomic and Metabolomic Labeling Strategies. *Angew. Chem., Int. Ed.* **2010**, *49*, 2680. (g) Leverett, C. A.; Purohit, V. C.; Johnson, A. G.; Davis, R. L.; Tantillo, D. J.; Romo, D. Dyotropic Rearrangements of Fused Tricyclic β-Lactones: Application to the Synthesis of (−)-Curcumanolide A and (−)-Curcumalactone. *J. Am. Chem. Soc.* **2012**, *134*, 13348. (h) Christenson, J. K.; Robinson, S. L.; Engel, T. A.; Richman, J. E.; Kim, A. N.; Wackett, L. P. OleB from Bacterial Hydrocarbon Biosynthesis Is a β-Lactone Decarboxylase That Shares Key Features with Haloalkane Dehalogenases. *Biochemistry.* **2017**, *56*, 5278. (i) Robinson, S. L.; Christenson, J. K.; Wackett, L. P. Biosynthesis and chemical diversity of β-lactone natural products. *Nat. Prod. Rep.* **2019**, *36*, 458.

(2) (a) Tamai, Y.; Yoshiwara, H.; Someya, M.; Fukumoto, J.; Miyano, S. Asymmetric [2 + 2] Cycloaddition of Ketene with Aldehydes catalysed by Chiral Bissulfonamide-Trialkylaluminium Complexes. *J. Chem. Soc. Chem. Commun.* **1994**, 2281. (b) Wan, Z.; Nelson, S. G. Catalytic Asymmetric Propionate Aldol Reactions via Acyl Halide−Aldehyde Cyclocondensations. *Org. Lett.* **2000**, *2*, 1883. (c) Zhu, C.; Shen, X.; Nelson, S. G. Cinchona Alkaloid-Lewis Acid Catalyst Systems for Enantioselective Ketene-Aldehyde Cycloadditions. *J. Am. Chem. Soc.* **2004**, *126*, 5352. (d) Gnanadesikan, V.; Corey, E. J. Enantioselective β-Lactone Formation from Ketene and Aldehydes Catalyzed by a Chiral Oxazaborolidine. *Org. Lett.* **2006**, *8*, 4943. (e) Kull, T.; Peters, R. Practical Enantioselective Synthesis of β-Lactones Catalyzed by Aluminum Bissulfonamide Complexes. *Adv. Synth. Catal.* **2007**, *349*, 1647. (f) Kull, T.; Peters, R. Contact Ion Pair Directed Lewis Acid Catalysis: Asymmetric Synthesis of *trans*-Configured β-Lactones. *Angew. Chem., Int. Ed.* **2008**, *47*, 5461.

(3) (a) Wynberg, H.; Staring, E. G. J. Asymmetric Synthesis of (*S*)- and (*R*)-Malic Acid from Ketene and Chloral. *J. Am. Chem. Soc.* **1982**, *104*, 166. (b) Wynberg, H.; Staring, E. G. J. Catalytic Asymmetric Synthesis of Chiral 4-Substituted 2-Oxetanones. *J. Org. Chem.* **1985**, *50*, 1977. (c) Tennyson, R.; Romo, D. Use of In Situ Generated Ketene in the Wynberg β-Lactone Synthesis: New Transformations of the Dichlorinated β-Lactone Products. *J. Org. Chem.* **2000**, *65*, 7248. (d) Armstrong, A.; Geldart, S. P.; Jenner, C. R.; Scutt, J. N. Organocatalytic Synthesis of β-Alkylaspartates via β-Lactone Ring Opening. *J. Org. Chem.* **2007**, *72*, 8091. (e) Mondal, M.; Ibrahim, A. A.; Wheeler, K. A.; Kerrigan, N. J. Phosphine-Catalyzed Asymmetric Synthesis of β-Lactones from Arylketoketenes and Aromatic Aldehydes. *Org. Lett.* **2010**, *12*, 1664. (f) Ibrahim, A. A.; Nalla, D.; Van Raaphorst, M.; Kerrigan, N. J. Catalytic Asymmetric Heterodimerization of Ketenes. *J. Am. Chem. Soc.* **2012**, *134*, 2942.

(4) (a) Nelson, S. G.; Peelen, T. J.; Wan, Z. Catalytic Asymmetric Acyl Halide-Aldehyde Cyclocondensations: A Strategy for Ensantioselective Catalyzed Cross Aldol Reactions. *J. Am. Chem. Soc.* **1999**, *121*, 9742. (b) Zhu, C.; Shen, X.; Nelson, S. G. Cinchona Alkaloid-Lewis Acid Catalyst Systems for Enantioselective Ketene-Aldehyde Cycloadditions. *J. Am. Chem. Soc.* **2004**, *126*, 5352. (c) Calter, M. A.; Tretyak, O. A.; Flaschenriem, C. Formation of Disubstituted β-Lactones Using Bifunctional Catalysis. *Org. Lett.* **2005**, *7*, 1809. (d) Kull, T.; Peters, R. Contact Ion Pair Directed Lewis Acid Catalysis: Asymmetric Synthesis of *trans*-Configured β-Lactones. *Angew. Chem., Int. Ed.* **2008**, *47*, 5461.

(5) (a) Dymock, B. W.; Kocienski, P. J.; Pons, J. M. 3-(Trimethylsilyl)oxetan-2-ones via Enantioselective [2 + 2] Cycloaddition of (Trimethylsily1)ketene to Aldehydes Catalysed by Methylaluminoimidazoline. *Chem. Commun.* **1996**, 1053. (b) Yang, H. W.; Romo, D. Studies of the Asymmetric [2 + 2] Cycloaddition of Silylketenes and Aldehydes Employing Ti-TADDOL Catalysts. *Tetrahedron Lett.* **1998**, *39*, 2877. (c) Evans, D. A.; Janey, J. M. C_2-Symmetric Cu(II) Complexes as Chiral Lewis Acids. Catalytic, Enantioselective Cycloadditions of Silyl Ketenes. *Org. Lett.* **2001**, *3*, 2125. (d) He, L.; Lv, H.; Zhang, Y.; Ye, S. Formal Cycloaddition of Disubstituted Ketenes with 2-Oxoaldehydes Catalyzed by Chiral N-Heterocyclic Carbenes. *J. Org. Chem.* **2008**, *73*, 8101. (e) Wang, X.; Shao, P.; Lv, H.; Ye, S. Enantioselective Synthesis of β-Trifluoromethyl-β-lactones via NHC-Catalyzed Ketene-Ketone Cycloaddition Reactions. *Org. Lett.* **2009**, *11*, 4029. (f) Wang, X.; Zhang, Y.; Ye, S. Enantioselective Synthesis of Spirocyclic Oxindole-β-lactones via N-Heterocyclic Carbene-Catalyzed Cycloaddition of Ketenes and Isatins. *Adv. Synth. Catal.* **2010**, *352*, 1892. (g) Douglas, J.; Taylor, J. E.; Churchill, G.; Slawin, A. M. Z.; Smith, A. D. NHC-Promoted Asymmetric β-Lactone Formation from Arylalkylketenes and Electron-Deficient Benzaldehydes or Pyridinecarboxaldehydes. *J. Org. Chem.* **2013**, *78*, 3925. (h) Hao, X.; Liu, X.; Li, W.; Tan, F.; Chu, Y.; Zhao, X.; Lin, L.; Feng, X. Chiral Lewis Acid Catalyzed Asymmetric Cycloadditions of Disubstituted Ketenes for the Synthesis of β-Lactones and δ-Lactones. *Org. Lett.* **2014**, *16*, 134. (i) Douglas, J. J.; Churchill, G.; Slawin, A. M. Z.; Fox, D. J.; Smith, A. D. Stereo- and Chemodivergent NHC-Promoted Functionalisation of Arylalkylketenes with Chloral. *Chem. Eur. J.* **2015**, *21*, 16354.

(6) (a) Mo, J.; Yang, R.; Chen, X.; Tiwari, B.; Chi, Y. R. Direct α-Functionalization of Simple Aldehydes via Oxidative N-Heterocyclic Carbene Catalysis. *Org. Lett.* **2013**, *15*, 50. (b) Davies, A. T.; Slawin, A. M. Z.; Smith, A. D. Enantioselective NHC-Catalyzed Redox [2 + 2] Cycloadditions with Perfluoroketones: A Route to Fluorinated Oxetanes. *Chem. Eur. J.* **2015**, *21*, 18944.

(7) (a) Cortez, G. S.; Tennyson, R. L.; Romo, D. Intramolecular, Nucleophile-Catalyzed Aldol-Lactonization (NCAL) Reactions: Catalytic, Asymmetric Synthesis of Bicyclic β-Lactones. *J. Am. Chem. Soc.* **2001**, *123*, 7945. (b) Oh, S. H.; Cortez, G. S.; Romo, D. Asymmetric Synthesis of Bicyclic β-Lactones via the Intramolecular, Nucleophile-Catalyzed Aldol Lactonization: Improved Efficiency and Expanded Scope. *J. Org. Chem.* **2005**, *70*, 2835. (c) Henry-Riyad, H.; Lee, C.; Purohit, V. C.; Romo, D. Bicyclic- and Tricyclic-β-lactones via Organonucleophile-Promoted Bis-Cyclizations of Keto Acids: Enantioselective Synthesis of (+)-Dihydroplakevulin. *Org. Lett.* **2006**, *8*, 4363. (d) Purohit, V. C.; Matla, A. S.; Romo, D. Concise Synthesis of Spirocyclic, Bridged γ-Butyrolactones via Stereospecific, Dyotropic Rearrangements of β-Lactones Involving 1,2-Acyl and δ-Lactone Migrations. *J. Am. Chem. Soc.* **2008**, *130*, 10478. (e) Morris, K. A.; Arendt, K. M.; Oh, S. H.; Romo, D. Double Diastereoselective, Nucleophile-Catalyzed Aldol Lactonizations (NCAL) Leading to β-Lactone Fused Carbocycles and Extensions to β-Lactone Fused Tetrahydrofurans. *Org. Lett.* **2010**, *12*, 3764. (f) Leverett, C. A.; Purohit, V. C.; Romo, D. Enantioselective, Organocatalyzed, Intramolecular AldolLactonizations with Keto Acids Leading to Bi- and Tricyclic β-Lactones and Topology-Morphing Transformations. *Angew. Chem., Int. Ed.* **2010**, *49*, 9479. (g) Kong, W.; Romo, D. Diastereo- and Enantioselective Synthesis of Bi- and Tricyclic N-Heterocycle-Fused β-Lactones. *J. Org. Chem.* **2017**, *82*, 13161.

(8) (a) Calter, M. A. Catalytic, Asymmetric Dimerization of Methylketene. *J. Org. Chem.* **1996**, *61*, 8006. (b) Calter, M. A.; Orr, R. K.; Song, W. Cinchona Alkaloid-Lewis Acid Catalyst Systems for Enantioselective Ketene-Aldehyde Cycloadditions. *Org. Lett.* **2003**, *5*, 4745. (c) Purohit, V. C.; Richardson, R. D.; Smith, J. W.; Romo, D. Practical, Catalytic, Asymmetric Synthesis of β-Lactones via a Sequential Ketene Dimerization/Hydrogenation Process: Inhibitors of the Thioesterase Domain of Fatty Acid Synthase. *J. Org. Chem.* **2006**, *71*, 4549.

(9) (a) Yeh, P.-P.; Daniels, D. S. B.; Cordes, D. B.; Slawin, A. M. Z.; Smith, A. D. Isothiourea-Mediated One-Pot Synthesis of Trifluoromethyl Substituted 2-Pyrones. *Org. Lett.* **2014**, *16*, 964. (b) Davies, A. T.; Pickett, P. M.; Slawin, A. M. Z.; Smith, A. D. Asymmetric Synthesis of Tri- and Tetrasubstituted Trifluoromethyl Dihydropyranones from α-Aroyloxyaldehydes via NHC Redox Catalysis. *ACS*

https://doi.org/10.1021/acs.joc.2c02688
J. Org. Chem. XXXX, XXX, XXX−XXX

Catal. **2014**, *4*, 2696. (c) Young, C. M.; Elmi, A.; Pascoe, D. J.; Morris, R. K.; McLaughlin, C.; Woods, A. M.; Frost, A. B.; de la Houpliere, A.; Ling, K. B.; Smith, T. K.; Slawin, A. M. Z.; Willoughby, P. H.; Cockroft, S. L.; Smith, A. D. The Importance of 1,5-Oxygen··· Chalcogen Interactions in Enantioselective Isochalcogenourea Catalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 3705.

(10) Morrill, L. C.; Douglas, J.; Lebl, T.; Slawin, A. M. Z.; Fox, D. J.; Smith, A. D. Isothiourea-Mediated Asymmetric Michael-Lactonisation of Trifluoromethylenones: a Synthetic and Mechanistic Study. *Chem. Sci.* **2013**, *4*, 4146.

(11) Zhang, S.; Greenhalgh, M. D.; Slawin, A. M. Z.; Smith, A. D. Tandem Sequential Catalytic Enantioselective Synthesis of Highly-Functionalised Tetrahydroindolizine Derivatives. *Chem. Sci.* **2020**, *11*, 3885.

(12) Wang, Y.; Young, C. M.; Liu, H.; Hartley, W. C.; Weinhold, M.; Cordes, D. B.; Slawin, A. M. Z.; Smith, A. D. A Desilylative Approach to Alkyl Substituted C(1)-Ammonium Enolates: Application in Enantioselective [2 + 2] Cycloadditions. *Angew. Chem., Int. Ed.* **2022**, *61*, e202208800.

(13) Nakagawa, Y.; Chanthamath, S.; Fujisawa, I.; Shibatomi, K.; Iwasa, S. Ru(II)-Pheox-Catalyzed Si−H Insertion Reaction: Construction of Enantioenriched Carbon and Silicon Centers. *Chem. Commun.* **2017**, *53*, 3753.

(14) Antunez, D. B.; Greenhalgh, M. D.; Brueckner, A. C.; Walden, D. M.; Elías-Rodríguez, P.; Roberts, P.; Young, B.; West, T. W.; Slawin, A. M. Z.; Cheong, P. H-Y.; Smith, A. D. Catalytic Enantioselective Synthesis of Perfluoroalkyl-substituted β-lactones via a Concerted Asynchronous [2 + 2]- Cycloaddition: A Synthetic and Computational Study. *Chem. Sci.* **2019**, *10*, 6162.

(15) For discussions of S···O interactions in isothiourea catalysis: (a) Birman, V. B.; Li, X.; Han, Z. Nonaromatic Amidine Derivatives as Acylation Catalysts. *Org. Lett.* **2007**, *9*, 37. (b) Liu, P.; Yang, X.; Birman, V. B.; Houk, K. N. Origin of Enantioselectivity in Benzotetramisole-Catalyzed Dynamic Kinetic Resolution of Azlactones. *Org. Lett.* **2012**, *14*, 3288. (c) Abbasov, M. E.; Hudson, B. M.; Tantillo, D. J.; Romo, D. Acylammonium Salts as Dienophiles in Diels−Alder/Lactonization Organocascades. *J. Am. Chem. Soc.* **2014**, *136*, 4492. (d) Robinson, E. R. T.; Walden, D. M.; Fallan, C.; Greenhalgh, M. D.; Cheong, P. H.-Y.; Smith, A. D. Non-Bonding 1,5-S···O Interactions Govern Chemo- and Enantioselectivity in Isothiourea-Catalyzed Annulations of Benzazoles. *Chem. Sci.* **2016**, *7*, 6919. (e) Greenhalgh, M. D.; Smith, S. M.; Walden, D. M.; Taylor, J. E.; Brice, Z.; Robinson, E. R. T.; Fallan, C.; Cordes, D. B.; Slawin, A. M. Z.; Richardson, H. C.; Grove, M. A.; Cheong, P. H.-Y.; Smith, A. D. A C═O···Isothiouronium Interaction Dictates Enantiodiscrimination in Acylative Kinetic Resolutions of Tertiary Heterocyclic Alcohols. *Angew. Chem., Int. Ed.* **2018**, *57*, 3200. For use of S···O interaction in asymmetric synthesis: (f) Nagao, Y.; Miyamoto, S.; Miyamoto, M.; Takeshige, H.; Hayashi, K.; Sano, S.; Shiro, M.; Yamaguchi, K.; Sei, Y. Highly Stereoselective Asymmetric Pummerer Reactions That Incorporate Intermolecular and Intramolecular Nonbonded S···O Interactions. *J. Am. Chem. Soc.* **2006**, *128*, 9722. For examples of S···O interactions in medicinal chemistry: (g) Beno, B. R.; Yeung, K.-S.; Bartberger, M. D.; Pennington, L. D.; Meanwell, N. A. A Survey of the Role of Noncovalent Sulfur Interactions in Drug Design. *J. Med. Chem.* **2015**, *58*, 4383. For a discussion on the origin of chalcogen-bonding interactions: (h) Pascoe, D. J.; Ling, K. B.; Cockroft, S. L. The Origin of Chalcogen-Bonding Interactions. *J. Am. Chem. Soc.* **2017**, *139*, 15160. For an excellent short overview, see: (i) Breugst, M.; Koenig, J. J. σ-Hole Interactions in Catalysis. *Eur. J. Org. Chem.* **2020**, *2020*, 5473.

(16) For a review of 1,5-chalcogen bonding interactions in organoselenium chemistry, see: (a) Mukherjee, A. J.; Zade, S. S.; Singh, H. B.; Sunoj, R. B. Organoselenium Chemistry: Role of Intramolecular Interactions. *Chem. Rev.* **2010**, *110*, 4357. For selected examples in catalysis, see: (b) Fujita, K.; Iwaoka, M.; Tomoda, S. Synthesis of Diaryl Diselenides Having Chiral Pyrrolidine Rings with C_2 Symmetry. Their Application to the Asymmetric Methoxyselenenylation of *trans*-β-Methylstyrenes. *Chem. Lett.* **1994**, *23*, 923. (c) Fujita, K.; Murata, K.; Iwaoka, M.; Tomoda, S. Asymmetric Intramolecular Selenoetherification and Selenolactonization using an Optically Active Diary1 Diselenide derived from D-Mannitol. *J. Chem. Soc. Chem. Commun.* **1995**, 1641. (d) Wirth, T. Asymmetric Reaction of Arylalkenes with Diselenides. *Angew. Chem., Int. Ed.* **1995**, *34*, 1726. (e) Fukuzawa, S.; Takahashi, K.; Kato, H.; Yamazaki, H. Asymmetric Methoxyselenenylation of Alkenes with Chiral Ferrocenylselenium Reagents. *J. Org. Chem.* **1997**, *62*, 7711. (f) Wirth, T.; Häuptli, S.; Leuenberger, M. Catalytic Asymmetric Oxyselenenylation−Elimination Reactions Using Chiral Selenium Compounds. *Tetrahedron: Asymmetry.* **1998**, *9*, 547. (g) Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. New Nitrogen Containing Chiral Diselenides: Synthesis and Asymmetric Addition Reactions to Olefins. *Tetrahedron: Asymmetry* **2000**, *11*, 4645. (h) Browne, D. M.; Niyomura, O.; Wirth, T. Catalytic Use of Selenium Electrophiles in Cyclizations. *Org. Lett.* **2007**, *9*, 3169. (i) Kawamata, Y.; Hashimoto, T.; Maruoka, K. A Chiral Electrophilic Selenium Catalyst for Highly Enantioselective Oxidative Cyclization. *J. Am. Chem. Soc.* **2016**, *138*, 5206.

(17) For an early theoretical investigation of chalcogen bonding, see: (a) Bleiholder, C.; Gleiter, R.; Werz, D. B.; Köppel, H. Theoretical Investigations on Heteronuclear Chalcogen−Chalcogen Interactions: On the Nature of Weak Bonds between Chalcogen Centers. *Inorg. Chem.* **2007**, *46*, 2249. For a recent review, see: (b) Gleiter, R.; Haberhauer, G.; Werz, D. B.; Rominger, F.; Bleiholder, C. From Noncovalent Chalcogen−Chalcogen Interactions to Supramolecular Aggregates: Experiments and Calculations. *Chem. Rev.* **2018**, *118*, 2010. For a perspective, see: (c) Kolb, S.; Oliver, G. A.; Werz, D. B. Chemistry Evolves, Terms Evolve, but Phenomena Do Not Evolve: From Chalcogen−Chalcogen Interactions to Chalcogen Bonding. *Angew. Chem., Int. Ed.* **2020**, *59*, 22306.

(18) For examples of chalcogen bonding catalysis, see: (a) Benz, S.; López-Andarias, J.; Mareda, J.; Sakai, N.; Matile, S. Catalysis with Chalcogen Bonds. *Angew. Chem, Int. Ed.* **2017**, *56*, 812. (b) Wonner, P.; Vogel, L.; Düser, M.; Gomes, L.; Kneip, F.; Mallick, B.; Werz, D. B.; Huber, S. M. Carbon−Halogen Bond Activation by Selenium-Based Chalcogen Bonding. *Angew. Chem, Int. Ed.* **2017**, *56*, 12009. (c) Wonner, P.; Vogel, L.; Kniep, F.; Huber, S. M. Catalytic Carbon−Chlorine Bond Activation by Selenium-Based Chalcogen Bond Donors. *Chem. Eur. J.* **2017**, *23*, 16972. (d) Wonner, P.; Dreger, A.; Vogel, L.; Engelage, E.; Huber, S. M. Chalcogen Bonding Catalysis of a Nitro-Michael Reaction. *Angew. Chem., Int. Ed.* **2019**, *58*, 16923. (e) Wang, W.; Zhu, H.; Liu, S.; Zhao, Z.; Zhang, L.; Hao, J.; Wang, Y. Chalcogen−Chalcogen Bonding Catalysis Enables Assembly of Discrete Molecules. *J. Am. Chem. Soc.* **2019**, *141*, 9175. (f) Wang, W.; Zhu, H.; Feng, L.; Yu, Q.; Hao, J.; Zhu, R.; Wang, Y. Dual Chalcogen−Chalcogen Bonding Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 3117.

(19) Crimmin, J.; O'Hanlon, P. J.; Rogers, N. H. The Chemistry of Pseudomonic Acid. Part 7. Stereochemical Control in the Preparation of C-2-substituted Monic Acid Esters via the Peterson Olefination. *J. Chem. Soc., Perkin Trans.* **1985**, 541.

(20) Shtelman, A. V.; Becker, J. Y. A Convenient Method for the Synthesis of a-Silylacetic Acids. *Tetrahedron Lett.* **2008**, *49*, 3101.

https://doi.org/10.1021/acs.joc.2c02688
J. Org. Chem. XXXX, XXX, XXX−XXX