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α-Haloenol Acetates: Versatile Reactants for Oxetan-2-one, Azetidin-2-one and Isoxazolidin-5-one Synthesis

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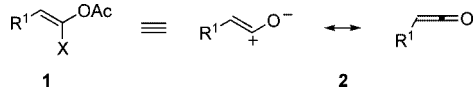
New ketene equivalents, namely α-haloenol acetates, are investigated as both nucleophilic and electrophilic reactants in a tandem aldol–lactonization reaction. Diethylaluminum ethoxide proves to be an efficient promoter for the aldol reaction with a wide range of substrates, including inter alia, aldehydes, ketones, imines, nitrones and oximes, leading to oxetan-2-ones, azetidin-2-ones and isoxazolidin-5-ones. The resultant heterocyclic adducts are common structural elements in numerous compounds of interest as well as key intermediates in the preparation of other functionalities.

Introduction

Oxetan-2-ones, azetidin-2-ones and isoxazolidin-5-ones are witnessing a great deal of interest because of their synthetic applications and their potential use as therapeutic agents.[1] Useful reactions exploiting the inherent strain in the four-membered rings and their transformation into β-hydroxy and β-amino acids have been widely developed.[2,3] As units present in many natural products, β-amino acids, β-hydroxy acids, β-lactones and β-lactams are of great importance. Since the first preparation of β-lactams by Staudinger et al. in 1907 by a [2+2] cycloaddition between ketenes and imines,[4] many synthetic methods for the preparation of β-lactones and β-lactams have been investigated.[5] Amongst these methods, the tandem aldol–lactonization reaction has been applied to a wide variety of carbon skeleton constructions.[6] Though the aldol reaction with silyl enol ethers generally takes place smoothly and gives the adducts in satisfactory yields,[7] typical Lewis acid catalysts sometimes induce side reactions such as cleavage of protecting groups, isomerization and rearrangement. The formation of side reactions is more or less avoided with more stable reactants such as enol esters. There are many reports of aldol reactions that employ enol esters under basic conditions; however, to date, only a few aldol reactions proceeding under weakly acidic or neutral conditions have been reported.[8] Recently, Mukaiyama et al. explored a new and effective catalyst, diethylaluminum ethoxide, which promotes aldol reactions starting from enol esters.[9,10] As part of our investigation of organochromium methodology, we described an efficient synthesis of α-haloenol acetates **1** by using chromous chloride.[11] The use of diethylaluminum ethoxide brought us to report herein a tandem aldol–lactonization reaction starting from α-haloenol acetates **1** that behave as a ketene equivalent (**2**; Scheme 1).



1 2

Scheme 1. α-Haloenol acetates **1** and their synthetic equivalence with ketenes.

Results and Discussion

Besides the expected reactions of a ketene equivalent with nucleophilic moieties,[12] such as hydrolysis (Scheme 2, Reaction a), alcoholysis (Reaction b)[11] and aminolysis (Reaction c), α-haloenol acetates **1** are capable of undergoing aldol reactions with electrophilic moieties such as aldehydes and ketones (Scheme 3, Reactions d, e and f), imines (Reaction g), nitrones (Reaction h) and oximes (Reaction i).[13] We found that freshly prepared diethylaluminum ethoxide was an efficient promoter for the aldol reaction starting from α-haloenol acetates **1**.

When the aliphatic derivative of α-chloroenol ester, (*Z*)-1-chloro-4-phenylbutenylacetate (**1a**), and aliphatic aldehydes or ketones **3** are reacted with diethylaluminum ethoxide in anhydrous THF, di- and tri-substituted β-lactones **4** were obtained in moderate-to-good yields (Table 1, Entries

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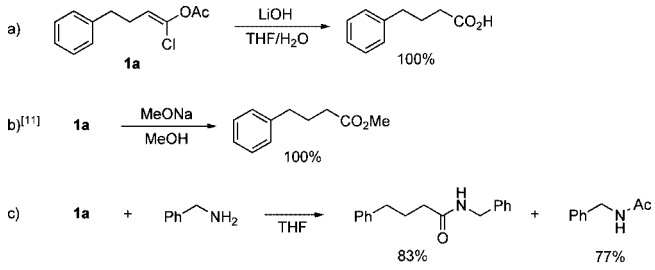
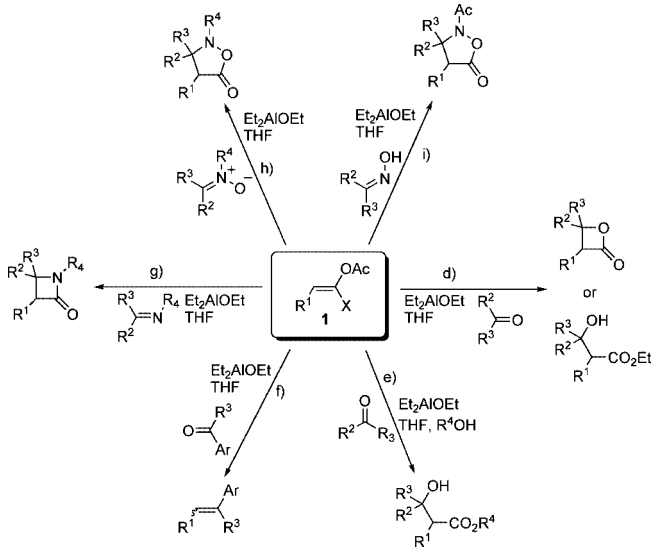


Scheme 2. Reactivities of α-haloenol acetates with nucleophiles.

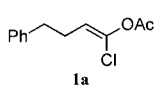
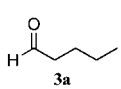
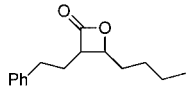
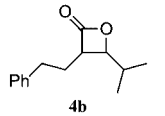
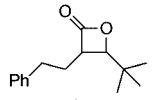
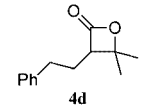
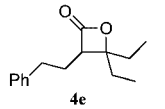
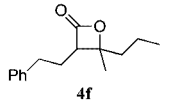
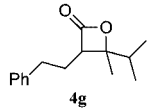
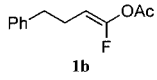
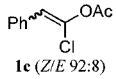
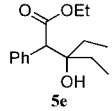
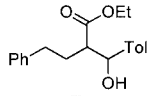
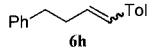
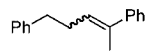
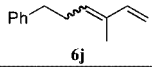


Scheme 3. Reactivities of α-haloenol acetates with electrophiles.

1–7).[14] The range of suitable α-haloenol acetates encompassed (*Z*)-1-fluoro-4-phenylbut-1-enyl acetate (**1b**) that provide access to β-lactones, though in lower but acceptable yield (Entry 8). When reacted under the same conditions, the aryl derivative of the α-chloroenol ester, 1-chloro-2-phenylethenyl acetate (**1c**), affords β-hydroxy ester **5e** (Entry 9). The reaction of aliphatic derivatives of the α-chloroenol ester also gives rise to β-hydroxy esters **5** when the reaction is carried out in a mixture of THF and alcohol (Entry 10). Interestingly, the aldol reaction can take place in protic solvents. Finally, reaction of **1a** with α,β-unsaturated carbonyl compounds led to di- and tri-substituted olefins **5** (Entries 11–14).

When reacted with imines, (*Z*)-1-chloro-4-phenylbutenyl acetate (**1a**) gives rise to β-lactams **7** and β-amino esters **9** (Table 2, Entries 1–4). Unfortunately, bicyclic azetidin-2-one derivative **8d** (Entry 4) could not be isolated, but could be detected by ^{1}H NMR analysis of the crude material: it decomposes to acyclic amide **10d**. Unexpectedly, tricyclic compound **11d** could be isolated as a byproduct. The α-haloenol esters proved also to be reactive with nitrones and oximes **12**. Under standard conditions, **1a** affords isoxazolidin-5-ones **13** in good yields (Entries 5–7). Interestingly, from oximes, *N*-acetyl-isoxazolidin-5-ones are obtained

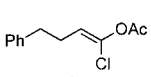
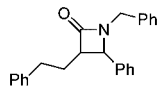
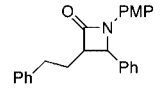
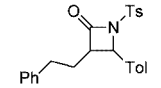
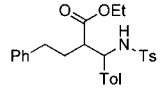
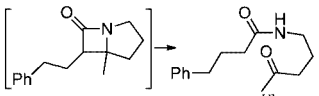
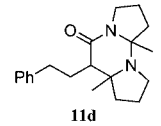
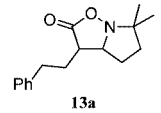
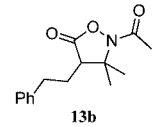
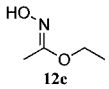
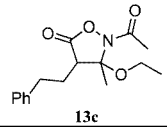
Table 1. Reaction of **1** with carbonyl compounds.

Entry	α-Haloenol acetate	Carbonyl	Adduct	Yield[a] (corrected yield)[b] [%]
1	 **1a**	 **3a**	 **4a**	63 (72) *cis*/*trans* 70:30
2	**1a**	 **3b**	 **4b**	67 (76) *cis*/*trans* 35:65
3	**1a**	 **3c**	 **4c**	68 (76) *cis*/*trans* 50:50
4	**1a**	 **3d**	 **4d**	80 (87)
5	**1a**	 **3e**	 **4e**	69 (74)
6	**1a**	 **3f**	 **4f**	74 (82) *cis*/*trans* 33:66
7	**1a**	 **3g**	 **4g**	68 (74) *cis*/*trans* 6:94
8	 **1b**	**3g**	**4g**	52 *cis*/*trans* 21:79
9	 **1c** (*Z*/*E* 92:8)	**3e**	 **5e**	60 (65)[c]
10[d]	**1a**	Tol—CHO **3h**	 **5h**	85 *syn*/*anti* 70:30
11	**1a**	**3h**	 **6h**	68 *E*/*Z* 86:14
12	**1b**	**3h**	**6h**	82 *E*/*Z* 63:37
13	**1a**	 **3i**	 **6i**	52 *E*/*Z* 70:30
14	**1a**	 **3j**	 **6j**	[e]

[a] Isolated yield after SiO_2 chromatographic purification. Stereochemistries have been deduced from ^{1}H NMR analysis. [b] Corrected yield based on conversion of α-haloenol acetate. [c] Unreacted **1c** was recovered as a mixture of isomers *Z*/*E* 67:33. [d] Solvent: THF/EtOH. [e] Unstable adduct.

(Entries 6 and 7). Alkoxy-substituted isoxazolidin-5-one **13c** also decomposed on silica gel to give the isoxazol-5(2*H*)-one derivative through β-elimination of ethanol (Entry 7).

Table 2. Reaction of **1** with imines, nitrones and oximes.

Entry	α-Haloenol acetate	Electrophile	Adduct	Yield[a] (corrected yield)[b] [%]
1	 **1a**	 **7a**	 **8a**	73 (77) *cis*/*trans* 12:88
2	**1a**	 **7b**	 **8b**	30 (34) *cis*/*trans* 5:95
3a	**1a**	 **7c**	 **8c**	13[c] (19) *cis*/*trans* 50:50
3b	**1a**	 **7c**	 **9c**	29 (42) *cis*/*trans* 50:50
4a	**1a**	 **7d**	 **8d**	**10d**[d]
4b	**1a**	 **7d**	 **11d**	25
5	**1a**	 **12a**	 **13a**	60 (65) *cis*/*trans* 80:20
6	**1a**	 **12b**	 **13b**	65
7	**1a**	 **12c**	 **13c**	80[e] *cis*/*trans* > 98:2

[a] Isolated yield after SiO_2 chromatographic purification. Stereochemistries have been deduced from ^1H NMR analysis. [b] Corrected yield based on conversion of α-haloenol acetate. [c] Yield calculated from ^1H NMR of the crude material. [d] Compound **8d** could not be isolated. It gives quantitatively *N*-(4-oxopentyl)-4-phenylbutanamide. [e] Compound **13c** undergoes a β-elimination on SiO_2 to give 5(2*H*)-isoxazolone as a byproduct.

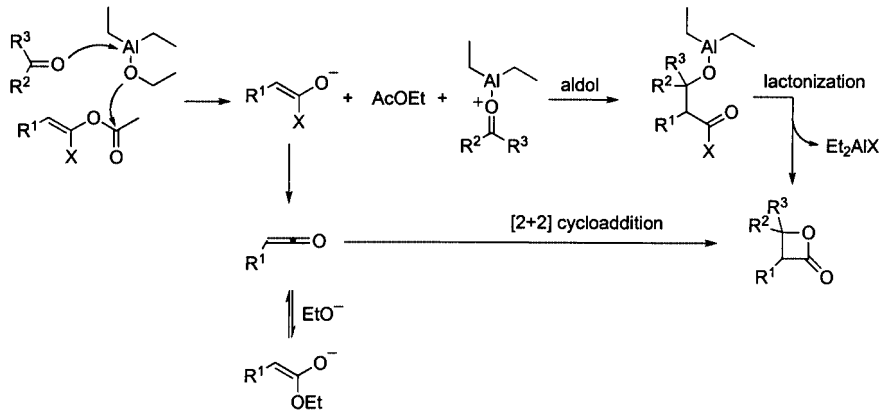
The scope of the reaction was explored by using various aliphatic carbonyl derivatives and the results indicate intriguing stereoselectivity. A reversal of stereoselectivity was observed between a few linear and branched aldehydes (Table 1, Entries 1 and 2). A better selectivity was observed with ketones with respect to aldehydes (Entries 2 and 7) and a bulky substituent did not lead to any selectivity (Entry 3). In addition, the stereoselectivity of β-lactones obtained from α-fluoroenol esters is lower than that obtained from α-chloroenol (Entries 7 and 8). These results cannot be rationalized by a simple stereochemical model. Mukayama et al. postulated that enol esters can be activated by nucleophilic attack of the acetyl group by the ethoxy group of Et_2AlOEt after coordination of the aluminum reagent to the ketone or the aldehyde (Scheme 4).[9] Thus, a one-,[15] or two-step acylation can give ethyl acetate as a byproduct. An aldol reaction followed by lactonization may then give rise to the β-lactone with elimination of diethylhaloalane. The conversion of the carboxylic acid halide enolate to the corresponding ketene may also give the β-lactone by a [2+2] cycloaddition.[16] Results obtained from α-fluoroenol acetate **1b** seem to exclude a common nucleophile, such as ketene **2**, if the reaction is not catalyzed by Et_2AlX or if it is in both cases irreversible. Alkylhaloalanes and alkylethoxyalanes readily form complexes of associated units through reversible and rather weak interactions.[17] Thus, several transition states may be involved depending on the steric interactions between the substituents. A transesterification of the aldol adduct or the conversion of the ketene to an ester enolate may explain the formation of β-hydroxy esters

When α-haloenol acetates are reacted with α,β-unsaturated aldehydes and ketones under standard conditions, di- and tri-substituted olefins **6** are obtained. A decarboxylation of the transcient β-lactone probably occurs, promoted by dialkylethoxyalane and dialkylhaloalane. β-Lactone could actually be detected by ^1H NMR analysis of the crude materials. Treatment of β-lactone **4k** with diethylaluminum ethoxide or dimethylaluminum chloride led to a mixture of β-lactone, β-hydroxy ester and olefin (Scheme 5). Decarboxylation occurs with aryl derivatives because of the electron density of the aryl group: it was actually demonstrated that electron-rich groups at the C-4 position of 2-oxetanones facilitate the decarboxylation reaction.[2a,18] Finally, the mechanism probably involves a stepwise fragmentation through a zwitterionic intermediate because both β-lactone fragmentations are nonstereoselective.

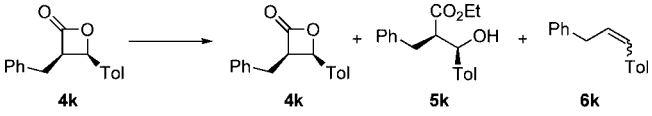
Besides the aldol reactions with electrophilic moieties, we finally observed the formation of a β-keto ester adduct formed by a Claisen-type condensation in the presence of DMSO (Scheme 6). The mechanism is not clear but can be interpreted as the Claisen condensation of two ethyl carboxylates, as the treatment of α-haloenol acetates with Et_2AlOEt may give rise to ethyl carboxylate derivatives.

Conclusions

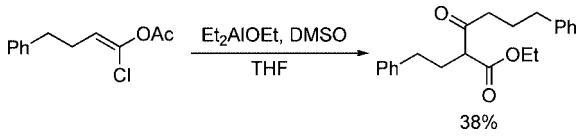
α-Haloenol acetates proved to be versatile reactants and diethylaluminum ethoxide demonstrated a powerful promotion of aldol and tandem aldol–lactonization reactions with formal [2+2] and [2+3] cycloadditions. Thus, the reaction of aldehydes and ketones under the described conditions provide access to β-lactones, β-hydroxy esters and olefins according to the substitution pattern. Under the same conditions, imines give rise to β-amino esters and β-lactams, and isoxazolidin-5-ones could be obtained starting from nitrones and oximes. Further extensions are underway in our laboratory, including the enantioselective synthesis of



Scheme 4. Activation of the enol acetate by Et_2AlOEt.



Scheme 5. Decarboxylation of 2-oxetanones promoted by Et_2AlOEt and Me_2AlCl.



Scheme 6. Claisen condensation.

oxetan-2-ones, azetidin-2-ones and isoxazolidin-5-ones through optically active dialkylaluminum alkoxide, which is readily accessible from chiral alcohols.

Experimental Section

Triethylaluminum (25% in toluene) was purchased from Aldrich. Tetrahydrofuran (THF) was distilled from Na/benzophenone ketyl. GC–MS analyses were carried out with a Shimadzu GCMS-QP5050A instrument with a SGE silica capillary, 25 m × 0.22 mm BPX5 column (5% phenyl polysilphenylene-siloxane/95% methylpolysiloxane), helium carrier gas (29 mL/min; 113 kPa), 260 °C interface, 80 °C column temp., 320 °C detector, programmed for 2 min at 80 °C, then heating.

4-Butyl-3-(2-phenylethyl)oxetan-2-one (4a) (Representative Procedure): To a solution of triethylaluminum (25% in toluene, 0.75 mL) was carefully added anhydrous ethanol (73 μL, 1.25 mmol) at –78 °C under an argon atmosphere. The solution was warmed to room temp. and diluted with anhydrous THF (2.0 mL). (*Z*)-1-Chloro-4-phenylbut-1-enyl acetate (**1a**) (50 μL, 0.25 mmol) and valeraldehyde (**3a**) (54 μL, 0.5 mmol) were then added to the solution of diethylaluminum ethoxide, at 0 °C under an argon atmosphere. After the reaction mixture was stirred for 15 h from 0 °C to room temp., aqueous Rochelle salt and AcOEt were added, and the mixture was stirred for an additional 30 min at room temp. The layers were separated, and the aqueous phase was extracted twice with AcOEt. The combined organic extracts were washed with brine and then dried with Na_2SO_4. After concentration under vacuum, the crude product was purified by chromatography on silica gel to afford 37 mg (63%) of 4-butyl-3-(2-phenylethyl)oxetan-2-one (**4a**) (*cis*/*trans* 70:30) as a colorless oil. **4a:** ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.18 (m, 5 H), 4.56–4.46 (m, 0.7 H_{cis}), 4.24–4.15 (m, 0.3 H_{trans}), 3.69–3.57 (m, 0.7 H_{cis}), 3.24.3.13 (m, 0.3 H_{trans}), 2.98–2.65 (m, 2 H), 2.30–1.34 (m, 8 H), 0.93 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 172.2 (*cis*), 171.5 (*trans*), 140.7 (*cis*), 140.4 (*trans*), 128.7, 128.6, 128.5, 126.6 (*trans*), 126.5 (*cis*), 78.5 (*trans*), 75.8 (*cis*), 55.5 (*trans*), 51.8 (*cis*), 34.1 (*trans*), 33.5 (*cis*), 33.2 (*trans*), 30.1 (*cis*), 29.7 (*trans*), 27.8 (*cis*), 27.2 (*trans*), 25.9 (*cis*), 22.5 (*cis*), 22.4 (*trans*), 14.0 ppm. IR: $\tilde{\nu}$ = 1821 cm^{-1}. HRMS (IE): calcd. for $C_{15}H_{20}O_2$ $[M]^+$ 232.1463; found 232.1467.

4-Isopropyl-3-(2-phenylethyl)oxetan-2-one (4b): (*trans*/*cis* 65:35). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.19 (m, 5 H), 4.09 (dd, J_1 = 10.6 Hz, J_2 = 6.2 Hz, 0.35 H_{cis}), 3.96 (dd, J_1 = 7.8 Hz, J_2 = 4.1 Hz, 0.65 H_{trans}), 3.62 (m, 0.35 H_{cis}), 3.25 (td, J_1 = 7.8 Hz, J_2 = 4.1 Hz, 0.65 H_{trans}), 3.07–2.97 (m, 0.35 H_{cis}), 2.88–2.70 (m, 1.65 H), 2.27–1.84 (m, 3 H), 1.07 (d, J = 6.9 Hz, 1.05 H_{cis}), 1.04 (d, J = 6.9 Hz, 1.95 H_{trans}), 0.95 (d, J = 6.9 Hz, 1.95 H_{trans}), 0.92 (d, J = 6.9 Hz, 1.05 H_{cis}) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.1 (*cis*), 171.4 (*trans*), 140.8 (*cis*), 140.4 (*trans*), 128.7, 128.4, 126.5 (*cis*), 126.4 (*trans*), 82.9 (*trans*), 80.3 (*cis*), 53.5 (*trans*), 51.1 (*cis*), 33.2 (*cis*), 33.1 (*trans*), 32.3 (*trans*), 30.0 (*trans*), 29.0 (*cis*), 26.3 (*cis*), 19.2 (*cis*), 18.0, 17.2 (*trans*) ppm. IR: $\tilde{\nu}$ = 1821 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{18}O_2$ $[M]^+$ 218.1307; found 218.1305.

4-*tert*-Butyl-3-(2-phenylethyl)oxetan-2-one (4c): (*cis*/*trans* 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 10 H), 4.21 (d, J = 6.8 Hz, 1 H_{cis}), 4.01 (J = 3.8 Hz, 1 H_{trans}), 3.67 (td, J_1 = 7.2 Hz, J_2 = 6.8 Hz, 1 H_{cis}), 3.33 (td, J_1 = 7.2 Hz, J_2 = 3.8 Hz, 1 H_{trans}), 3.07–2.97 (m, 1 H_{cis}), 2.86–2.68 (m, 3 $H_{cis+trans}$), 2.42–1.95 (m, 4 H), 1.06 (s, 9 H_{cis}), 1.00 (s, 9 H_{trans}) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.4 (*cis*), 171.4 (*trans*), 140.7 (*cis*), 140.5 (*trans*), 128.7, 128.4, 126.4, 85.2 (*trans*), 82.3 (*cis*), 51.5 (*cis*), 50.5 (*trans*), 34.2, (*cis*), 33.9 (*trans*), 33.1 (*cis*), 32.9 (*trans*), 30.4 (*trans*), 27.4 (*cis*), 26.0 (*cis*), 24.5 (*trans*) ppm. IR: $\tilde{\nu}$ = 1820 cm^{-1}. HRMS (IE): calcd. for $C_{15}H_{20}O_2$ $[M]^+$ 232.1463; found 232.1445.

4,4-Dimethyl-3-(2-phenylethyl)oxetan-2-one (4d): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37–7.19 (m, 5 H), 3.23 (dd, J_1 = 8.3 Hz, J_2 = 8.0 Hz, 1 H), 2.93–2.60 (m, 2 H), 2.30–1.85 (m, 2 H), 1.56 (s, 3 H), 1.48 ppm (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4, 140.5, 128.7, 128.6, 126.5, 80.2, 57.3, 33.4, 27.9, 26.9, 22.0 ppm.

IR: $\tilde{\nu}$ = 1812 cm^{-1}. HRMS (IE): calcd. for $C_{13}H_{16}O_2$ $[M]^+$ 204.1150; found 204.1172.

4,4-Diethyl-3-(2-phenylethyl)oxetan-2-one (4e): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 5 H), 3.24 (dd, J_1 = 9.0 Hz, J_2 = 7.2 Hz, 1 H), 2.95–2.84 (m, 1 H), 2.79–2.68 (m, 1 H), 2.22–2.10 (m, 1 H), 2.04–1.67 (m, 5 H), 1.02 (t, J = 7.5 Hz, 3 H), 0.92 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.0, 140.7, 128.7, 128.5, 126.5, 85.0, 56.0, 33.7, 29.3, 26.3, 24.9, 8.2, 7.6 ppm. IR: $\tilde{\nu}$ = 1814 cm^{-1}. HRMS (IE): calcd. for $C_{15}H_{20}O_2$ $[M]^+$ 232.1463; found 232.1467.

4-Methyl-3-(2-phenylethyl)-4-propyloxetan-2-one (4f): (*trans*/*cis* 66:33). *trans*-**4f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.19 (m, 5 H), 3.21 (dd, J_1 = 8.1 Hz, J_2 = 7.9 Hz, 1 H), 2.90–2.79 (m, 1 H), 2.76–2.65 (m, 1 H), 2.20–2.07 (m, 1 H), 1.97–1.66 (m, 3 H), 1.46 (s, 3 H), 1.43–1.27 (m, 2 H), 0.96 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.8, 140.6, 128.7, 128.6, 126.5, 82.4, 56.2, 43.1, 33.5, 27.0, 19.7, 17.7, 14.3 ppm. *cis*-**4f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.19 (m, 5 H), 3.22 (dd, J_1 = 8.9 Hz, J_2 = 7.3 Hz, 1 H), 2.92–2.82 (m, 1 H), 2.77–2.66 (m, 1 H), 2.20–2.07 (m, 1 H), 2.02–1.89 (m, 1 H), 1.84–1.70 (m, 1 H), 1.68–1.57 (m, 1 H), 1.52 (s, 3 H), 1.49–1.42 (m, 2 H), 0.97 ppm (t, J = 7.3 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.9, 140.7, 128.7, 128.6, 126.5, 82.3, 58.3, 37.4, 33.6, 26.3, 24.9, 17.2, 14.5 ppm. IR: $\tilde{\nu}$ = 1815 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{20}O_2$ $[M]^+$ 232.1463; found 232.1467; calcd. for $C_{14}H_{20}$ $[M - CO_2]^+$ 188.1565; found 188.1551.

***trans*-4-Isopropyl-4-methyl-3-(2-phenylethyl)oxetan-2one:** (*trans*/*cis* 94:6). *trans*-**4g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 5 H), 3.19 (dd, J_1 = 9.2 Hz, J_2 = 7.4 Hz, 1 H), 2.92–2.82 (m, 1 H), 2.77–2.66 (m, 1 H), 2.22–2.09 (m, 1 H), 2.03–1.81 (m, 2 H), 1.40 (s, 3 H), 1.02 (d, J = 6.9 Hz, 3 H), 0.91 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8, 140.7, 128.7, 128.5, 126.4, 85.1, 55.5, 37.6, 33.5, 27.1, 17.1, 16.6, 15.2 ppm. IR: $\tilde{\nu}$ = 1813 cm^{-1}. GC (heating at 10 °C/min): t_R = 9.20 min. HRMS (IE): calcd. for $C_{15}H_{20}O_2$ $[M]^+$ 232.1463; found 232.1467. *cis*-**4g**: GC (heating at 10 °C/min): t_R = 9.04 min.

Ethyl 3-Ethyl-3-hydroxy-2-phenylpentanoate (5e): M.p. 58–60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.44 (m, 2 H), 7.36–7.29 (m, 3 H), 4.22 (dq, J_1 = 10.9 Hz, J_2 = 7.2 Hz, 1 H), 4.07 (dq, J_1 = 10.9 Hz, J_2 = 7.2 Hz, 1 H), 3.77 (br. s, 1 H), 3.67 (s, 1 H), 1.65 (qd, J_1 = 7.5 Hz, J_2 = 2.8 Hz, 2 H), 1.33–1.07 (m, 2 H), 1.22 (t, J = 7.2 Hz, 3 H), 0.96 (t, J = 7.5 Hz, 3 H), 0.78 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.9, 135.2, 129.9, 128.4, 127.6, 77.4, 76.1, 61.1, 56.8, 32.0, 30.5, 29.1, 27.0, 22.8, 14.2, 14.1, 8.3, 7.6 ppm. IR: $\tilde{\nu}$ = 3508, 1710 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{15}H_{23}O_3$ $[M]^+$ 251.1642; found 251.1639.

Ethyl 2-(Hydroxy-*p*-tolylmethyl)-4-phenylbutanoate (5h): According to the general procedure using (*Z*)-1-chloro-4-phenylbut-1-enyl acetate (**1a**) (50 μL, 0.25 mmol) and **3h** (60 μL, 0.5 mmol) in THF (1.0 mL) and EtOH (1.0 mL), the title compound **5h** (66 mg, 85%) was obtained as a mixture of isomers (*syn*/*anti* = 70:30). *syn*-**5h**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30–7.10 (m, 9 H), 4.94 (d, J = 5.9 Hz, 1 H), 4.08 (q, J = 7.1 Hz, 2 H), 2.79–2.44 (m, 4 H), 2.35 (s, 3 H), 2.12–1.96 (m, 2 H), 1.18 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.8, 141.6, 138.6, 137.4, 129.1, 128.5, 128.4, 126.2, 126.0, 74.2, 60.7, 52.6, 33.8, 28.9, 21.2, 14.2 ppm. IR: $\tilde{\nu}$ = 3455, 1729 cm^{-1}. *anti*-**5h**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.29–7.06 (m, 9 H), 4.80 (dd, J_1 = 8.1 Hz, J_2 = 5.1 Hz, 1 H), 4.16 (q, J = 7.1 Hz, 2 H), 2.86–2.50 (m, 4 H), 2.34 (s, 3 H), 2.02–1.82 (m, 1 H), 1.73–1.58 (m, 1 H), 1.27 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.2, 141.3, 138.9, 137.9, 129.4, 128.5, 126.5, 126.1, 75.4, 60.8, 52.7, 33.5, 31.2, 21.3, 14.4 ppm. IR: $\tilde{\nu}$ = 3455, 1706 cm^{-1}.

4-Phenyl-1-*p*-tolylbut-1-ene (6h): (*E*/*Z* 86:14). (*E*)-**6h**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.36–7.09 (m, 9 H), 6.41 (d, J = 15.9 Hz, 1 H), 6.22 (dt, J_1 = 15.9 Hz, J_2 = 6.4 Hz, 1 H), 2.85–2.76 (m, 2 H), 2.60–2.48 (m, 2 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.0, 136.7, 135.1, 130.3, 129.3, 129.0, 128.6, 128.5, 126.0, 36.1, 35.0, 21.3 ppm. (*Z*)-**6h**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.31–7.15 (m, 9 H), 6.43 (d, J = 11.7 Hz, 1 H), 5.67 (dt, J_1 = 11.7 Hz, J_2 = 6.6 Hz, 1 H), 2.84–2.64 (m, 4 H), 2.36 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.9, 136.4, 134.8, 131.3, 129.4, 129.0, 128.8, 128.6, 128.5, 126.0, 36.3, 30.6, 21.3 ppm.

2,5-Diphenylprop-2-ene (6i): (*E*/*Z* 70:30). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.43–7.13 (m, 10 H), 5.86 (t, J = 7.0 Hz, 0.7 H_E), 5.54 (t, J = 7.2 Hz, 0.3 H_Z), 2.86–2.77 (m, 1.4 H_E), 2.73–2.50 (m, 2 H_{E+Z}), 2.39–2.27 (m, 0.6 H_Z), 2.06 (s, 0.9 H_Z), 2.02 (s, 2.1 H_E) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.0 (*Z*), 142.1 (*E*), 137.0 (*Z*), 135.6 (*E*), 128.62, 128.59, 128.5, 128.33, 128.28, 128.2, 128.0, 127.5, 126.8, 126.7, 126.6, 126.0, 125.83, 125.76, 36.5 (*Z*), 36.0 (*E*), 31.1 (*Z*), 30.9 (*E*), 25.7 (*Z*), 15.9 (*E*) ppm.

(*E*)-(4-Methyl-3,5-hexadienyl)benzene [(*E*)-6j]: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.19 (m, 5 H), 6.38 (dd, J_1 = 17.3 Hz, J_2 = 10.6 Hz, 1 H), 5.55 (t, J = 7.2 Hz, 1 H), 5.10 (d, J = 17.3 Hz, 1 H), 4.95 (d, J = 10.6 Hz, 1 H), 2.79–2.66 (m, 2 H), 2.54–2.43 (m, 2 H), 1.71 (s, 3 H) ppm. (*Z*)-**6j**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.19 (m, 5 H), 6.77 (dd, J_1 = 17.3 Hz, J_2 = 10.9 Hz, 1 H), 5.45 (t, J = 7.5 Hz), 5.21 (d, J = 17.3 Hz, 1 H), 5.09 (d, J = 10.9 Hz, 1 H), 2.79–2.66 (m, 2 H), 2.54–2.43 (m, 2 H), 1.83 (s, 3 H) ppm.

1-Benzyl-4-phenyl-3-(2-phenylethyl)azetidin-2-one (8a): (*trans*/*cis* 88:12) ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30–6.89 (m, 15 H), 4.92 (d, J = 14.9 Hz, 0.12 H_{cis}), 4.86 (d, J = 14.9 Hz, 0.88 H_{trans}), 4.62 (d, J = 5.4 Hz, 0.12 H_{cis}), 4.07 (d, J = 2.0 Hz, 0.88 H_{trans}), 3.90 (d, J = 14.9 Hz, 0.12 H_{cis}), 3.75 (d, J = 14.9 Hz, 0.88 H_{trans}), 3.47–3.36 (m, 0.12 H_{cis}), 3.14–3.05 (m, 0.88 H_{trans}), 2.74 (t, J = 7.8 Hz, 1.76 H), 2.55–1.76 (m, 2.24 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 141.1, 137.8, 135.8, 129.1, 128.9, 128.6, 128.5, 127.8, 126.7, 126.1, 60.8, 60.0, 44.4, 33.4, 30.6 ppm. IR: $\tilde{\nu}$ = 1751 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{24}H_{24}N_1O_1$ $[M]^+$ 342.1852; found 342.1872. *trans*-**8a**: GC (heating at 25 °C/min): t_R = 12.42 min. *cis*-**8a**: GC (heating at 25 °C/min): t_R = 12.60 min.

1-(4-Methoxyphenyl)-4-phenyl-3-(2-phenylethyl)azetidin-2-one (8b): (*trans*/*cis* 95:5): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.13 (m, 12 H), 6.79 (d, J = 9.1 Hz, 2 H), 5.17 (d, J = 5.9 Hz, 0.05 H_{cis}), 4.63 (d, J = 2.2 Hz, 0.95 H_{trans}), 3.75 (s, 3 H), 3.14 (td, J_2 = 6.5 Hz, J_2 = 2.2 Hz, 0.95 H_{trans}), 2.85 (t, J = 7.2 Hz, 1.9 H_{trans}), 2.36–2.12 (m, 1.9 H_{trans}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 156.0, 141.0, 138.1, 131.5, 129.2, 128.6, 126.3, 126.1, 61.6, 60.1, 55.5, 33.5, 30.9 ppm. IR: $\tilde{\nu}$ = 1745 cm^{-1}. MS (CI, NH_3): *m*/*z* = 358 [M + H]$^+$. HRMS (ESI-TOF): calcd. for $C_{24}H_{24}N_1O_2$ $[M]^+$ 358.1802; found 358.1812. *trans*-**8b**: GC (heating at 25 °C/min): t_R = 13.60 min. *cis*-**8b**: GC (heating at 25 °C/min): t_R = 13.82 min.

3-(2-Phenylethyl)-4-*p*-tolyl-1-(*p*-tolylsulfonyl)azetidin-2-one (8c): (*cis*/*trans* 1:1): The β-lactam cannot be separated from *N*-(4-methylbenzylidene)-*p*-toluenesulfonamide by column chromatography. Characteristic peaks: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.17 (d, J = 6.6 Hz, 1 H_{cis}), 4.66 (d, J = 2.9 Hz, 1 H_{trans}), 3.43 (td, J_1 = 8.3 Hz, J_2 = 6.6 Hz, 1 H_{cis}), 3.12 (td, J_1 = 7.7 Hz, J_2 = 2.9 Hz, 1 H_{trans}) ppm.

Ethyl 4-Phenyl-2-[*p*-Tolyl(*p*-tolylsulfonylamino)methyl]butanoate (9c): (*syn*/*anti* 1:1): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (d, J = 8.1 Hz, 2 H), 7.30–7.18 (m, 3 H), 7.11–7.01 (m, 4 H), 6.92–6.82 (m, 4 H), 6.06 (d, J = 9.0 Hz, 0.5 H), 5.51 (d, J = 8.7 Hz, 0.5 H), 4.59 (dd, J_1 = 9.0 Hz, J_2 = 6.2 Hz, 0.5 H), 4.47 (dd, J_1 = 8.7 Hz, J_2 =

8.4 Hz, 0.5 H), 4.02 (q, J = 7.2 Hz, 1 H), 3.89 (q, J = 7.2 Hz, 1 H), 2.76–2.43 (m, 3 H), 2.33 (s, 1.5 H), 2.30 (s, 1.5 H), 2.25 (s, 3 H), 2.06–1.94 (m, 1 H), 1.80–1.67 (m, 1 H), 1.13 (t, J = 7.2 Hz, 1.5 H), 1.02 (t, J = 7.2 Hz, 1.5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 172.8, 143.1, 142.8, 141.1, 140.8, 138.1, 137.49, 137.45, 137.1, 136.0, 135.4, 129.3, 129.2, 129.02, 128.95, 128.5, 127.2, 127.0, 126.9, 126.4, 126.2, 126.1, 61.0, 60.8, 59.2, 58.5, 51.7, 51.4, 33.5, 33.2, 31.8, 30.4, 21.5, 21.1, 14.2, 14.0 ppm.

5-Methyl-6-(2-phenylethyl)-1-azabicyclo[3.2.0]heptan-7-one (8d): GC (heating at 25 °C/min): t_R = 9.43 min. MS (CI, NH_3): m/z = 230.

***N*-(4-Oxopentyl)-4-phenylbutanamide (10d):** ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.16 (m, 5 H), 5.67 (br. s, 1 H), 3.24 (td, J_1 = 6.8 Hz, J_2 = 5.9 Hz, 2 H), 2.65 (t, J = 7.3 Hz, 2 H), 2.50 (t, J = 6.8 Hz, 2 H), 2.21–2.13 (m, 2 H), 2.15 (s, 3 H), 2.04–1.88 (m, 2 H), 1.84–1.70 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 208.9, 173.0, 141.6, 128.6, 128.5, 126.1, 41.2, 39.1, 36.0, 35.3, 30.2, 27.2, 23.5 ppm. IR: $\tilde{\nu}$ = 1715, 1647 cm1. GC (heating at 25 °C/min): t_R = 10.10 min. MS (CI, NH_3): m/z = 248, 230. HRMS (ESI-TOF): calcd. for $C_{15}H_{22}N_1O_2$ $[M]^+$ 248.1645; found 248.1630.

6a,10a-Dimethyl-6-(2-phenylethyl)octahydrodipyrrolo[1,2-*a*:1′,2′-*c*]-pyrimidin-5(6*H*)-one (11d): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.16 (m, 5 H), 3.84–3.74 (m, 1 H), 3.52–3.43 (m, 1 H), 3.16–3.06 (m, 1 H), 2.93–2.88 (m, 2 H), 2.64–2.53 (m, 1 H), 2.29–2.16 (m, 2 H), 1.97–1.64 (m, 7 H), 1.46–1.32 (m, 2 H), 1.34 (s, 3 H), 0.84 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.8, 142.9, 128.8, 128.4, 125.8, 77.5, 65.1, 50.3, 47.4, 45.2, 43.2, 39.6, 35.8, 28.9, 25.2, 24.5, 24.2, 21.3 ppm. IR: $\tilde{\nu}$ = 1655 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{20}H_{29}N_2O_1$ $[M]^+$ 313.2274; found 313.2284.

6,6-Dimethyl-3-(2-phenylethyl)tetrahydropyrrolo[1,2-*b*]isoxazol-2(3*H*)-one (13a): (*cis*/*trans* 80:20). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.18 (m, 5 H), 4.13–4.05 (m, 0.8 H), 3.93–3.87 (m, 0.2 H), 3.21–3.12 (m, 0.8 H), 2.85–2.72 (m, 2 H), 2.71–2.61 (m, 0.2 H), 2.33–1.61 (m, 6 H), 1.41 (s, 3 H), 1.09 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.0, 140.6, 128.7, 128.5, 126.5, 69.9, 67.7, 45.5, 35.8, 33.9, 27.7, 25.9, 24.1, 23.9 ppm. IR: $\tilde{\nu}$ = 1768 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{16}H_{22}N_1O_2$ $[M]^+$ 260.1645; found 260.1630. *cis*-**13a**: GC (heating at 25 °C/min): t_R = 9.88 min. *trans*-**13a**: GC (heating at 25 °C/min): t_R = 10.10 min.

2-Acetyl-3,3-dimethyl-4-(2-phenylethyl)isoxazolidin-5-one (13b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.21 (m, 5 H), 3.13–3.03 (m, 1 H), 2.86–2.75 (m, 1 H), 2.68 (dd, J_1 = 9.7 Hz, J_2 = 4.4 Hz, 1 H), 2.15 (s, 3 H), 2.14–1.97 (m, 1 H), 1.80–1.63 (m, 1 H), 1.65 (s, 3 H), 1.35 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 171.4, 140.5, 128.7, 128.6, 126.5, 68.0, 50.9, 32.9, 26.3, 25.8, 23.1, 18.0 ppm. IR: $\tilde{\nu}$ = 1801, 1686 cm^{-1}. GC (heating at 25 °C/min): t_R = 9.05 min. MS (CI, NH_3): m/z = 262 $[M + H]^+$. HRMS (IE): calcd. for $C_{15}H_{19}NO_3$ $[M]^+$ 261.1365; found 261.1353; calcd. for $C_{13}H_{17}NO_2$ $[M - CH_2CO]^+$ 219.1259; found 219.1280.

2-Acetyl-3-ethoxy-3-methyl-4-(2-phenylethyl)isoxazolidin-5-one (13c): (*cis*/*trans* > 98:2; *trans* isomer could not be detected). *cis*-**13c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 5 H), 3.67 (dq, J_1 = 7.2 Hz, J_2 = 6.9 Hz, 1 H), 3.54 (dq, J_1 = 7.2 Hz, J_2 = 6.9 Hz, 1 H), 3.08–2.97 (m, 1 H), 2.89–2.78 (m, 1 H), 2.69 (dd, J_1 = 8.4 Hz, J_2 = 4.7 Hz, 1 H), 2.18 (s, 3 H), 2.19–2.04 (m, 1 H), 1.98–1.87 (m, 1 H), 1.88 (s, 3 H), 1.16 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 168.9, 140.7, 128.8, 128.6, 126.5, 95.2, 60.5, 50.9, 32.9, 25.4, 22.8, 20.9, 15.3 ppm. IR: $\tilde{\nu}$ = 1810, 1686 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{16}H_{21}N_1Na_1O_4$ $[M]^+$ 314.1363; found 314.1360.

Supporting Informations (see footnote on the first page of this article): Experimental procedures for hydrolysis, aminolysis, Claisen condensation, Ti(O*i*Pr)$_4$-mediated aldolization, commercial Et_2Al-OEt-mediated aldolization, Ti(O*i*Pr)$_3$Cl-mediated aldolization and decarboxylation reactions. Full characterization of isolated products and byproducts.

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