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Featured Article

Chiral 3-Acylglutaric Acid Derivatives from Strain-Induced Nucleophilic Retro-Claisen Ring-Opening Reactions

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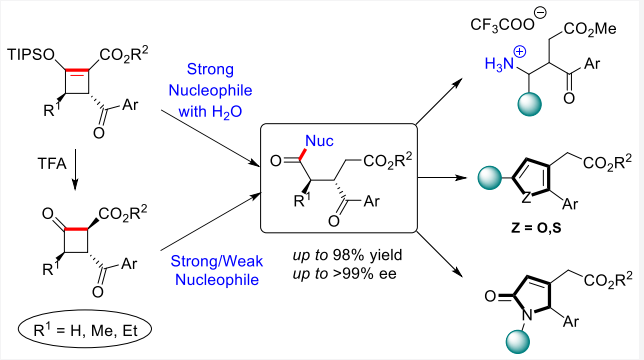
ABSTRACT: A nucleophilic retro-Claisen ring-opening of donor−acceptor cyclobutenes, formed with high stereocontrol by [3 + 1]-cycloaddition of TIPS-protected enoldiazoacetates with α-acyl sulfur ylides, has been developed. Removal of the TIPS group to form the isolable β-keto ester precedes the strain-induced ring-opening. Various amines, alcohols, thiols, and amino acid derivatives are effective nucleophiles, and their products are formed in very high yields via stoichiometric reactions. The chirality of the reactant donor−acceptor cyclobutenes is fully retained in the ring-opening reactions. The 3-acylglutaric acid products are converted to various valuable structures, including amido-diols, γ-aminobutyric acid (GABA) derivatives, and heterocycles.



INTRODUCTION

The use of strain energy to propel chemical reactions is a well-recognized strategy in chemistry and biology.[1,2] The ring-opening reactions of epoxides and aziridines are notable for their diverse uses and applications,[3] and donor−acceptor cyclopropanes[4] are employed for three-carbon homologation, including cycloaddition[5] and ring-opening reactions.[6] By contrast, ring-opening reactions of the cyclobutane ring, whose strain energy (26.3 kcal/mol) is similar to that of cyclopropane (27.5 kcal/mol),[7] would complement those of donor−acceptor cyclopropanes, but they have received far less attention.[8] Ring strain and C−C bond polarization by adjacent substituents provide zwitterionic character to these compounds, allowing them to undergo ring-opening cycloaddition and related transformations (Scheme 1a).[9] However, these reactions are limited by the need for strong polarizing substituents (A and D in Scheme 1a), and they have been amenable to asymmetric cycloaddition with the use of chiral catalysts in only one report.[10] Another approach to ring-opening reactions of strained organic compounds is the retro-Claisen reaction, which has a long history in chemical[11,12] and enzymatic[13] transformations. Despite their broad applications, however, this transformation has rarely been used for strain-induced ring-opening reactions.[14] Catalysts are required for ring-opening, and although access to achiral substrates is becoming convenient, chiral cyclobutane derivatives that may be appropriate for ring-opening reactions are rare.[15] There has been recent success in inducing chirality with chiral organocatalysis for a retro-Claisen reaction,[11b−d] but uncatalyzed ring-opening of chiral 2-oxocyclobutanecarboxylates by nucleophiles under mild conditions has not been explored.

Previous research from our laboratory established that catalytic [3 + 1]-cycloaddition of silyl group protected enoldiazoacetates with α-acyl sulfur ylides was effective in forming stable donor−acceptor cyclobutene derivatives (Scheme 1b).[16] This methodology produced 1,2,4-trisubstituted (R1 = H) and 1,2,3,4-tetrasubstituted (R1 = alkyl) 2-siloxycyclobutenecarboxylates in good yields with high diastereo- and enantiocontrol. Removal of the silyl protecting group from these cyclobutene derivatives would produce their β-keto esters suitable for strain-induced retro-Claisen reactions, and nucleophilic ring-opening could effectively cleave the C−C bond by Nuc-H addition (Scheme 1c).

We previously reported this ring-opening process with the corresponding 2-azetines-2-carboxylates,[17] but the same reaction conditions were unsuitable for retro-Claisen reactions of the more stable donor−acceptor cyclobutenes, and the reported 2-azetine ring-opening required the use of 2 equiv of the reactant nucleophile. We now report the ring-opening reactions of silyl-group protected donor−acceptor cyclobutenes with only 1 equiv of nucleophile, using only a stoichiometric amount of water to remove the silyl group.

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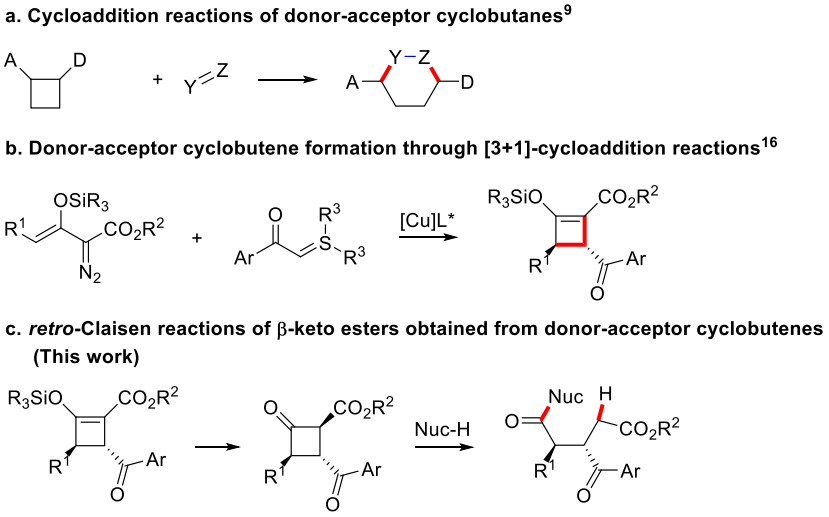
Scheme 1. Donor–Acceptor Cyclobutanes and Formation and Ring-Opening of Donor–Acceptor Cyclobutenes

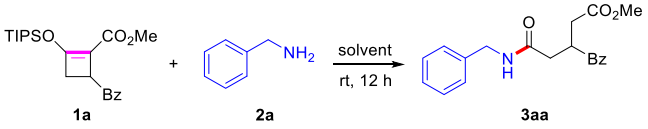


RESULTS AND DISCUSSION

Development of the Ring-Opening Reaction. In our previous report, the 2-azetine-2-carboxylate ring could be opened by various nucleophiles in DCM or THF/H_2O system.[17] However, under similar conditions, donor–acceptor cyclobutenes failed to deliver the desired product smoothly when using 2 equiv of benzylamine as the nucleophile, giving the ring-opened product in low yields in DCM and THF/H_2O. To determine the optimum conditions for the retro-Claisen reaction of donor–acceptor cyclobutenes, we screened the reaction of previously reported[16] TIPS-protected donor–acceptor cyclobutene **1a** with 2 equiv of benzylamine (**2a**) in different solvents under a standard set of conditions. As shown in Table 1, reactions performed in solvents including ethyl acetate, acetone, acetonitrile, and nitromethane gave much better results than did DCM or THF/H_2O (1:1, v/v). Among these solvents, nitromethane gave a nearly quantitative isolated yield of ring-opened product **3aa**, and after complete conversion of **1a**, about 1 equiv of benzylamine (**2a**) remained (entry 12). In a separate experiment, we reduced the amount of benzylamine to 1.05 equiv and once again obtained **3aa** in nearly quantitative yield (entry 13). In acetonitrile, the alternative dipolar aprotic solvent, with 1.05 equiv of benzylamine, the yield of **3aa** was only moderate, and reactants remained after the 12 h reaction time (entry 14).

Because only 1 equiv of benzylamine appeared to be required, and the nitromethane solvent was not dried before use, we considered that water in nitromethane (~0.1%), instead of benzylamine, removed the silyl group. Therefore, we used rigorously dried nitromethane as the solvent and used 1.05 equiv of benzylamine to perform the reaction. As anticipated, only a 43% yield of ring-opened product **3aa** was isolated after 24 h, and 54% of the reactant nucleophile remained after chromatographic isolation (Table 2). This result is consistent with our previously established use of one nucleophile (water) to remove the protective TIPS group and a second nucleophile to undergo the ring-opening of 2-azetine-2-carboxylates.[17] With 2 equiv of benzylamine in dry nitromethane, **3aa** was obtained in only 76% yield after 36 h with 20% of unreacted **1a** remaining, suggesting a slow rate for

Table 1. Solvent Screening of Ring-Opening Reaction of Donor–Acceptor Cyclobutene 1a with Benzylamine[a]

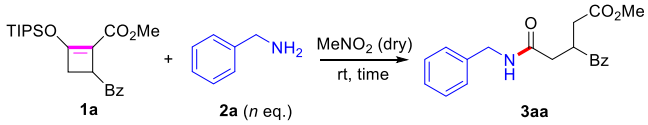


1a **2a** **3aa**

entry	solvent	yield **3aa** (%)
1	DCM	trace
2	THF/H_2O (1:1, v/v)	trace[c]
3	THF (with 1 equiv of H_2O)	72
4	THF (dry)	67
5	DMSO	ND
6	DMF	43
7	toluene	39
8	EtOAc	77
9	acetone	91
10	MeOH	ND
11	MeCN	95
12	$MeNO_2$	98
13[b]	$MeNO_2$	97
14[b]	MeCN	60

[a]Unless otherwise noted, the reaction conditions were as follows: **1a** (0.1 mmol, 1.0 equiv) and **2a** (2.0 equiv) in 2.0 mL of solvent at room temperature for 12 h. Isolated yields are reported. nd = not detected. Bz = benzoyl. [b]With 1.05 equiv of **2a**. [c]The solubility of **1a** was limited.

Table 2. Role of Water in Ring-Opening Reaction in Nitromethane[a]



1a **2a** (*n* eq.) **3aa**

entry	*n*	time	additive	yield **3aa** (%)
1	1.05	24	none	43
2	2.05	36	none	76
3	1.05	9	H_2O (1.0 equiv)	98

[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv) and **2a** (*n* equiv) in dry $MeNO_2$ (2.0 mL) at room temperature for the indicated time. Isolated yields are reported. Bz = benzoyl.

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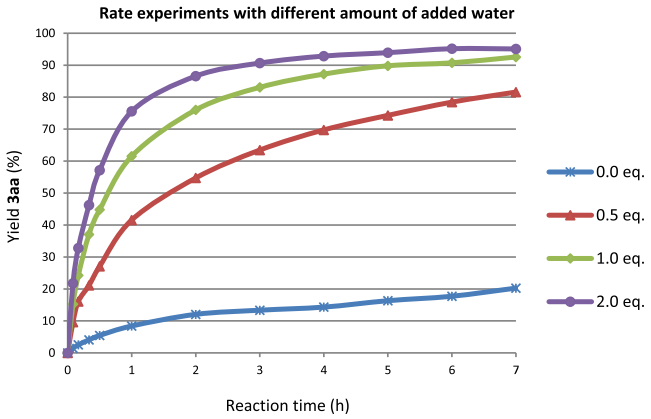
silyl group removal by this nucleophile. However, by adding 1 equiv of water to dry nitromethane with only 1 equiv of benzylamine, the reaction raced to completion within only 9 h in nearly quantitative isolated yield. In this system water (or hydroxide generated from water and the amine), and not benzylamine, removes the silyl group, and does so with significant rate acceleration over reactions performed without added water.

To further assess the rate acceleration associated with the addition of water, we performed rate experiments with 0−2 equiv of water added into the system (Scheme 2). Water

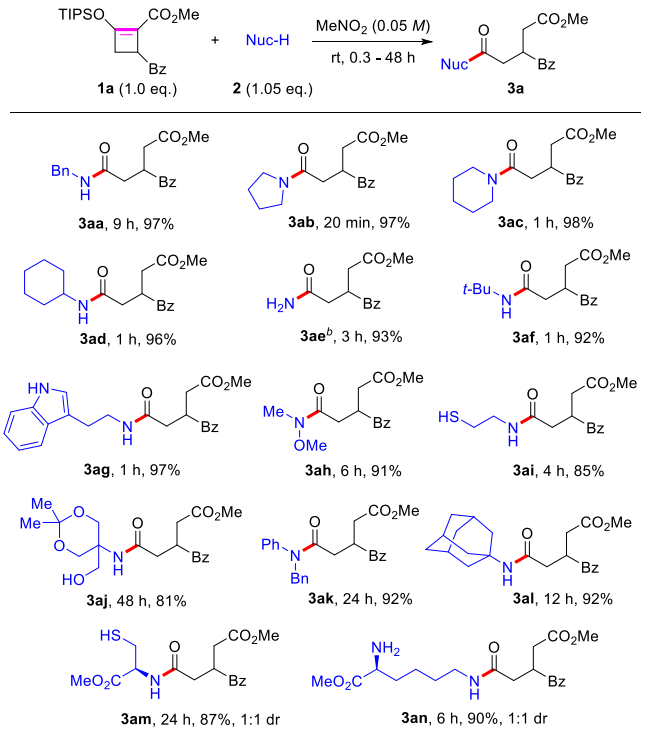
Scheme 2. Rate Experiments in Nitromethane at Room Temperature for the Conversion of 1a to 3aa with Benzylamine and Different Amounts of Added Water



greatly accelerates the rate of reaction, and only 0.5 equiv of water may be sufficient to deliver a high product yield for this nucleophilic ring-opening reaction. The conditions most favorable for product formation with stoichiometric reactants are those with 1.0−2.0 equiv of water in nitromethane, although even 0.5 equiv of water significantly increased the rate of ring opening. The rate acceleration by limited amounts of water is consistent with desilylation being the rate-limiting step in the overall transformation.

Scope of the Ring-Opening Reaction. With the optimized solvent conditions in hand, we screened representative amine nucleophiles **2** with racemic donor−acceptor cyclobutene **1a**, and the structures and yields of isolated ring-opening products are reported in Table 3. Primary and secondary amine nucleophiles **2** and ammonium hydroxide (**2e**) opened **1a** smoothly in nitromethane with excellent yields within 1 h, and with pyrrolidine (**2b**) the reaction was complete in only 20 min. Steric effects from congested primary amines (e.g., **3aj**) increased the reaction time. A Weinreb amide **3ah** was also formed in high yield through this ring-opening reaction. As occurred with the sole formation of **3aj** from the corresponding amino alcohol, in reactions with 2-sulfhydrylethylamine, only the amine functional group formed product (**3ai**). Amino esters were also effective, and cysteine derivative **3am** was obtained in high yield (89%) but with no diastereocontrol (dr = 1:1). L-Lysine methyl ester reacted selectively at the terminal amino group to afford ring-opening product **3an** in 90% isolated yield (dr = 1:1). Products from nucleophilic addition at the benzoyl carbonyl group were not evident in these reactions, nor were products from substitution on the ester.

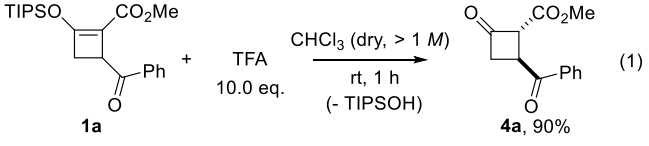
Table 3. Scope of Nucleophiles 2 in Ring-Opening of Racemic Donor−Acceptor Cyclobutene 1a[a]



[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv) and **2** (1.05 equiv) in wet $MeNO_2$ (~0.1% of water) (2.0 mL) at room temperature for the indicated time. Isolated yields are reported. Bz = benzoyl. [b]Ammonium hydroxide solution (29% NH_3 basis) was used.

Although aliphatic amines underwent the retro-Claisen reaction smoothly with donor−acceptor cyclobutene **1a**, aniline and representative alcohols did not. Using a stoichiometric amount of aniline under the standard reaction conditions, there was no detectable conversion of **1a** at a reaction time of more than 48 h. With alcohols, no reaction was observed after 48 h even when alcohol was the solvent. These results are consistent with desilylation being the rate-limiting step in the overall transformation, and they support the involvement of hydroxide as the nucleophile responsible for desilylation in the nucleophilic reactions with amines.

Accordingly, if the desilylation step was avoided by using the keto ester **4a**, an increase in the reaction rate for the retro-Claisen reaction could be anticipated, and if so, reactions might be able to be conducted in less polar solvents than nitromethane. To test this hypothesis, we examined conditions to convert **1a** to its corresponding β-keto ester. Among the desilylation methods attempted, we found TFA[18] in chloroform to be the most effective (eq 1), and β-keto ester **4a** was isolated in 90% yield by this method.



Using β-keto ester **4a** as the alternative to donor−acceptor cyclobutene **1a** for retro-Claisen reactions, ring-opening with benzylamine in nitromethane was achieved not only in nearly quantitative yield but also at a faster rate (within 2 h)

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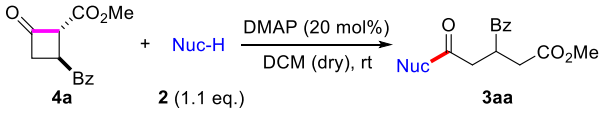
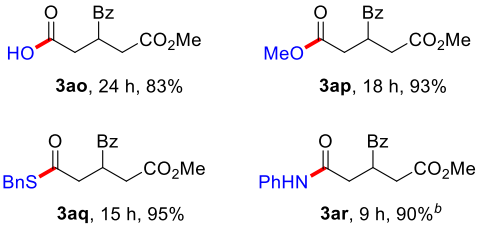
Scheme 3. Ring-Opening of the Alternative β-Keto Ester 4a with Weak Nucleophiles[a]





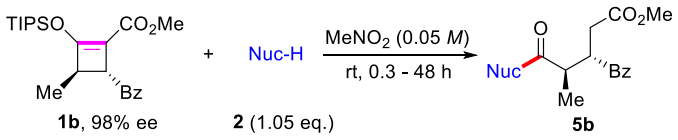
[a]Reaction conditions: **4a** (0.1 mmol, 1.0 equiv), DMAP (0.02 mmol, 0.2 equiv), and **2** (1.1 equiv) in dry DCM (1.0 mL) at room temperature for the indicated time. Isolated yields are reported. Bz = benzoyl. [b]With 10 mol % of DMAP.

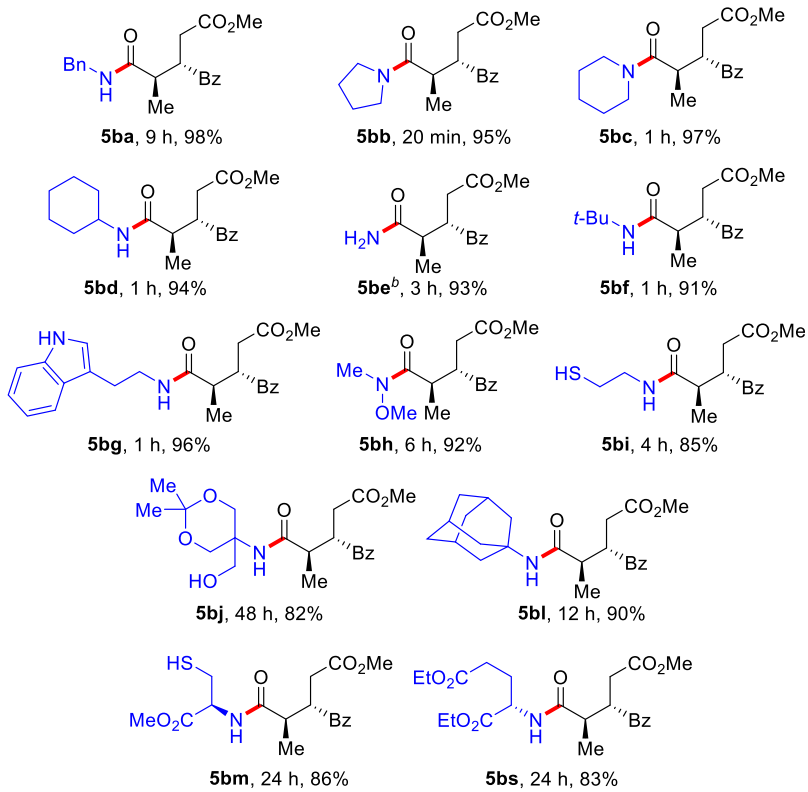
compared to that with the corresponding donor–acceptor cyclobutene (within 9 h). Notably, this reaction was complete at an even faster rate (within 1 h) in dichloromethane, suggesting the importance of nitromethane as the reaction solvent was in silyl group removal but not in the ring-opening reaction.

Since weakly nucleophilic substrates were unreactive with **1a**, we examined their ability to undergo retro-Claisen reactions with β-keto ester **4a**. Stoichiometric aniline (1.05 equiv), for example, which did not react with **1a** in either nitromethane or DCM at room temperature, underwent ring-opening with **4a** in DCM, albeit very slowly. After 60 h at room temperature the ring-opened product was obtained in only 78% yield (53% yield in $MeNO_2$) with reactants still remaining. Since aniline showed low reactivity, and less basic nucleophiles (e.g., alcohols and water) were certain to be even less reactive, we turned our attention to methods for further rate enhancements. Basic 4-dimethylaminopyridine (DMAP), which is well-known to catalytically activate acylation reactions,[19] was selected. We found that a catalytic amount of DMAP (10–20 mol %) in dry DCM allowed nucleophiles such as water, alcohols, thiols, and arylamines to undergo the ring-opening reaction in good to excellent yields (Scheme 3) at room temperature. However, even with this catalytic DMAP advantage, secondary alcohols failed to deliver the corresponding ester products.

In an effort to further understand the advantages of DMAP as an additive to enhance the retro-Claisen reaction, we examined its potential with silyl-protected **1a**. Using 2.0 equiv

Table 4. Scope of Nucleophiles 2 in Ring-Opening of Chiral Donor–Acceptor Cyclobutene 1b[a]





[a]Reaction conditions: **1b** (0.1 mmol, 1.0 equiv) and **2** (1.05 equiv) in wet $MeNO_2$ (~0.1% of water) (2.0 mL) at room temperature for the indicated time. Isolated yields are reported. Bz = benzoyl. [b]Ammonium hydroxide solution (29% NH_3 basis) was used.

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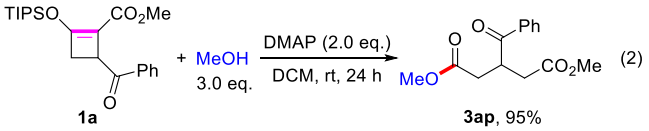
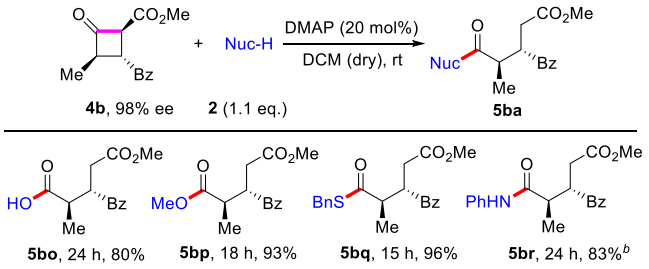
of DMAP with the donor–acceptor cyclobutene **1a**, methanol (3.0 equiv) was able to deliver the ring-opened ester **3ap** in 95% isolated yield within 24 h (eq 2). However, this alternative



methodology was not further pursued because of the required use of a large excess of nucleophile as well as higher than stoichiometric DMAP. As previously reported, chiral donor–acceptor cyclobutenes with high enantiomeric excess and diastereocontrol were conveniently obtained (Scheme 1b) by catalytic [3 + 1]-cycloaddition of enol diazoacetates with acyl ylides of sulfur.[16] To determine if optical purity is retained in the retro-Claisen ring-opening reaction, we treated *trans*-3-methyl **1b** (98% ee) with representative amines and in all cases examined (Table 4) the optical purity of the reactant retained in the ring-opened product. Furthermore, diastereocontrol was also retained; there was no evidence by spectral or chromatographic analysis of the diastereomer of the reported products. Isolated yields of ring-opened products from (3*R*,4*R*)-**1b** were virtually the same as those obtained with racemic **1a**, and reaction times were comparable. As reported for reactions with racemic **1a**, there was no evidence of imine formation with the benzoyl substituent, and steric factors influence the rate for ring-opening (e.g., **5bj**–**5bs**).

When using the corresponding *β*-keto ester **4b** as starting material, stoichiometric water, methanol, benzyl mercaptan, and aniline also delivered the ring-opening products **5bo**–**5br** under relatively dilute conditions with full retention of enantiomeric purity (Scheme 4). The lower yields obtained

Scheme 4. Ring-Opening of *β*-Keto Ester 4b with Weak Nucleophiles[a]

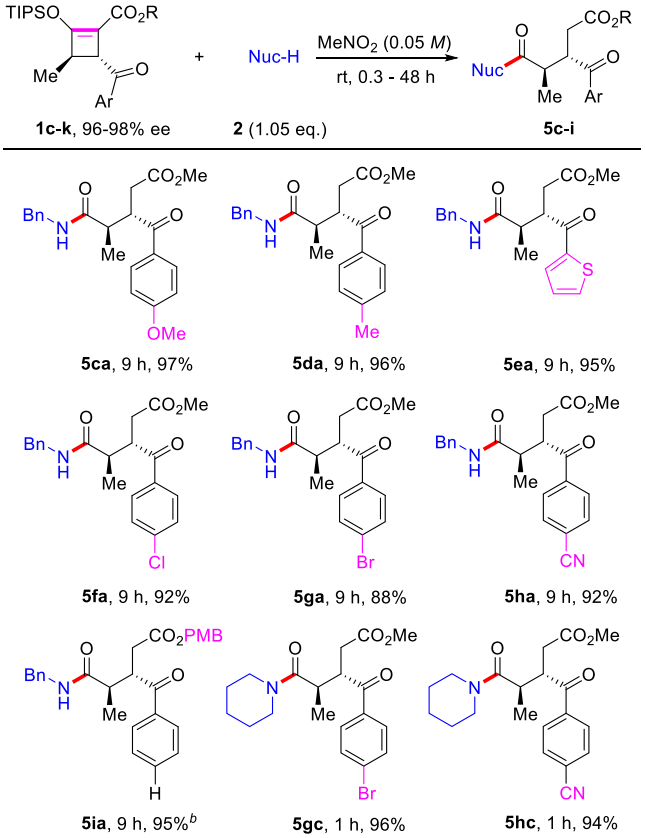


[a]Reaction conditions: **4b** (0.1 mmol, 1.0 equiv), DMAP (0.02 mmol, 0.2 equiv), and **2** (1.1 equiv) in dry DCM (1.0 mL) at room temperature for the indicated time. Isolated yields are reported. Bz = benzoyl. [b]With 10 mol % of DMAP.

for **5bo** and **5br** were due to problems with isolation rather than with nucleophilic reactivity. The success of the retro-Claisen reaction even with these model weak nucleophiles suggests very broad applicability.

We also varied benzoyl and ester substituents on the donor–acceptor cyclobutenes (3*R*,4*R*)-**1b**. High product yields of the ring-opened products (**5c**–**i**) were obtained from reactions with benzylamine (**2a**) and piperidine (**2c**), and optical purity was also retained in these reactions (Table 5). Product yields from donor–acceptor cyclobutenes with electron-donating (**1c**–**e**) and electron-withdrawing benzoyl substituents (**1f**–**h**) indicated no detectable electronic effect by these substituents

Table 5. Scope of Donor–Acceptor Cyclobutenes 1 in Ring-Opening with Benzylamine and Piperidine[a]



[a]Reaction conditions: **1** (0.1 mmol, 1.0 equiv) and **2** (1.05 equiv) in wet $MeNO_2$ (~0.1% of water) (2.0 mL) at room temperature for the indicated time. Isolated yields are reported. [b]PMB = *p*-methoxybenzyl.

on product yields, and the use of a PMB ester gave a similar product yield (**5ia**, 95%) as did the methyl ester (**5ba**, 98%, Table 4). Neither the substituted benzoyl group nor the ester were changed in these reactions to the limits of our detection.

As previously reported,[20] ethyl-substituted chiral donor–acceptor cyclobutene (3*R*,4*R*)-**1j** could be obtained with excellent diastereocontrol and 90% enantiomeric excess. We applied this cyclobutene in the retro-Claisen ring-opening with several aliphatic amines under standard reaction conditions (Scheme 5). As anticipated, products **5j** were obtained in excellent yields and with complete retention of enantiopurity. However, attempts to synthesize sterically more encumbered donor–acceptor cyclobutenes (R = *i*Pr or Bn instead of Me or Et) were not successful.

To demonstrate the practical utility of this method as a synthetic tool, we conducted scale-up reactions with pyrrolidine, tryptamine and methanol as the nucleophiles. The corresponding products, whose spectral characteristics matched those of the compounds obtained in the small-scale reactions, were obtained in excellent yields (Scheme 6).

To demonstrate the broad potential of the products from retro-Claisen ring-opening reactions of donor–acceptor cyclobutenes for the construction of diverse chemical libraries we examined several applicable transformations using racemic amide derivatives (Scheme 7). The reduction of **3ab** by $LiAlH_4$ (Scheme 7A) formed the corresponding amido diol **6** in high

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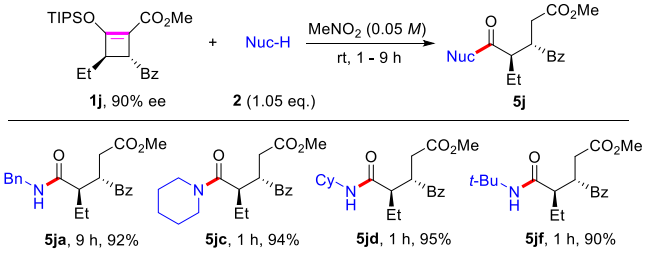
Scheme 5. Nucleophilic Retro-Claisen Ring-Opening of Donor–Acceptor Cyclobutene (3*R*,4*R*)-1j with Aliphatic Amines[a]

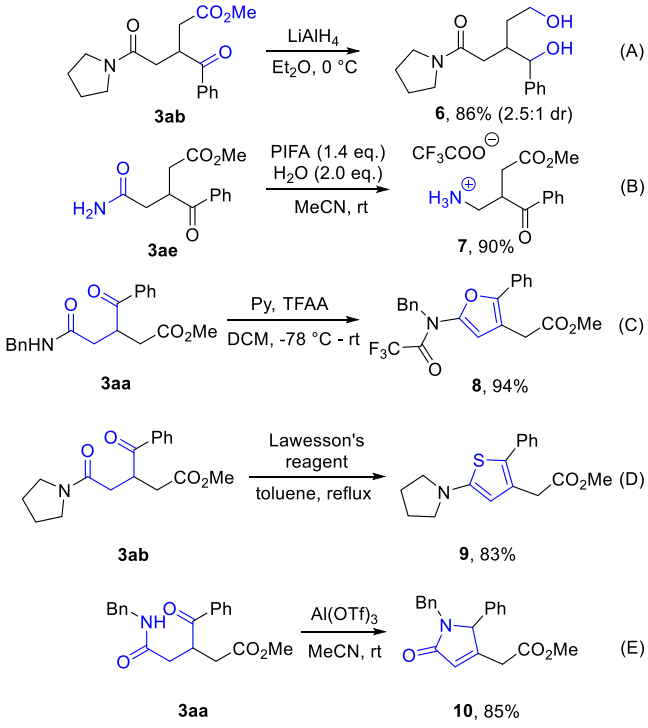


[a]Reaction conditions: **1** (0.1 mmol, 1.0 equiv) and **2** (1.05 equiv) in wet $MeNO_2$ (~0.1% of water) (2.0 mL) at room temperature for the indicated time. Isolated yields are reported. Bz = benzoyl.

yield (86%) but with low diastereocontrol (dr = 2.6:1). The amide functional group of **3ae** was converted to the corresponding γ-aminobutyric acid (GABA) derivative **7** in high yield by the Hofmann rearrangement using [bis-(trifluoroacetoxy)iodo]benzene (PIFA) (Scheme 7B).[21a] Because the amide products **3a** contain a 1,4-dicarbonyl structural unit, successful cyclization to furan **8** (Scheme 7C) using trifluoroacetic anhydride (TFAA) was achieved,[22] and thiophene **9** (Scheme 7D) was synthesized using Lawesson's reagent.[23] In addition, 1,5-dihydro-5-phenyl-2*H*-pyrrol-2-one **10** (Scheme 7E) was obtained in good yield using aluminum trifluoromethanesulfonate $Al(OTf)_3$ as the Lewis acid.[24] As demonstrated by these examples, the potential for the development of the retro-Claisen ring-opening of donor–acceptor cyclobutenes for a diversity of multifunctional platforms is extraordinary.

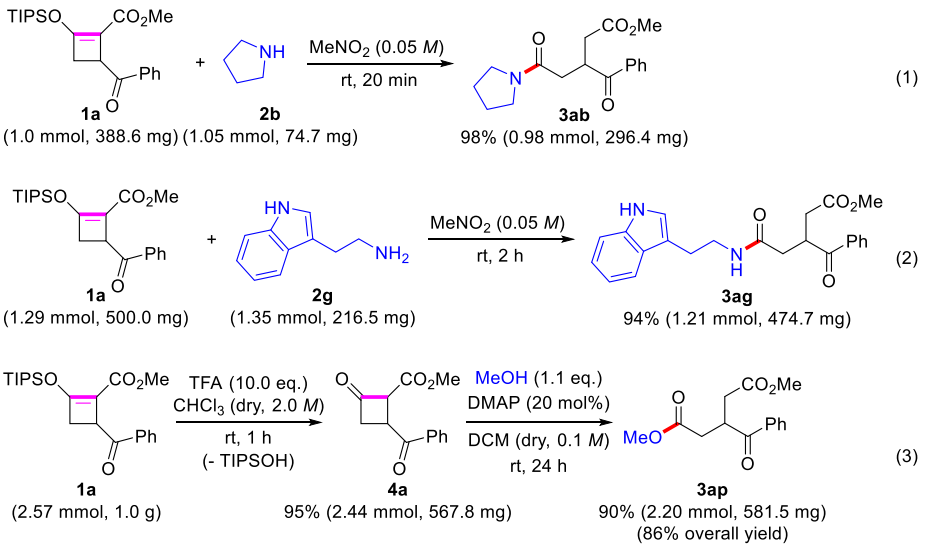
Reaction Mechanism. Analogous to the ring-opening of 2-azetine-2-carboxylates,[17] the mechanism for nucleophilic ring-opening of donor–acceptor 2-cyclobutene-2-carboxylates involves initial desilylation to form the intermediate β-keto ester that undergoes nucleophilic addition to the β-carbonyl group followed by ring-opening with proton capture to form the observed product (Scheme 8A). Several deuterium incorporation experiments were performed to investigate the role of water in the TIPS group removal and ring-opening. In

Scheme 7. Transformations of Ring-Opened Products 3a



the anticipated mechanism for nucleophilic addition/C–C bond cleavage for the retro-Claisen reaction (Scheme 8A), protonation at the carbon α to the carboxylate ester could come internally from the nucleophile or externally from water. To examine this step D_2O (5.0 equiv) was added to the mixture of **1a** and benzylamine (**2a**) in acetonitrile,[25] and ~65 mol % deuteration (1.3 D/two hydrogen positions) occurred at the α-position of the ester (Scheme 8B) suggesting that both intramolecular (from benzylamine) and intermolecular (from D_2O) transfer occurred in the ring-opening of the β-ketoester. On the other hand, ~52 mol % deuteration (1.04 D/two hydrogen positions) at the α-position of the ester occurred with pyrrolidine (**2b**) when 2 equiv of D_2O was added to the reaction mixture in dry nondeuterated acetonitrile (Scheme

Scheme 6. Scale-up Reactions



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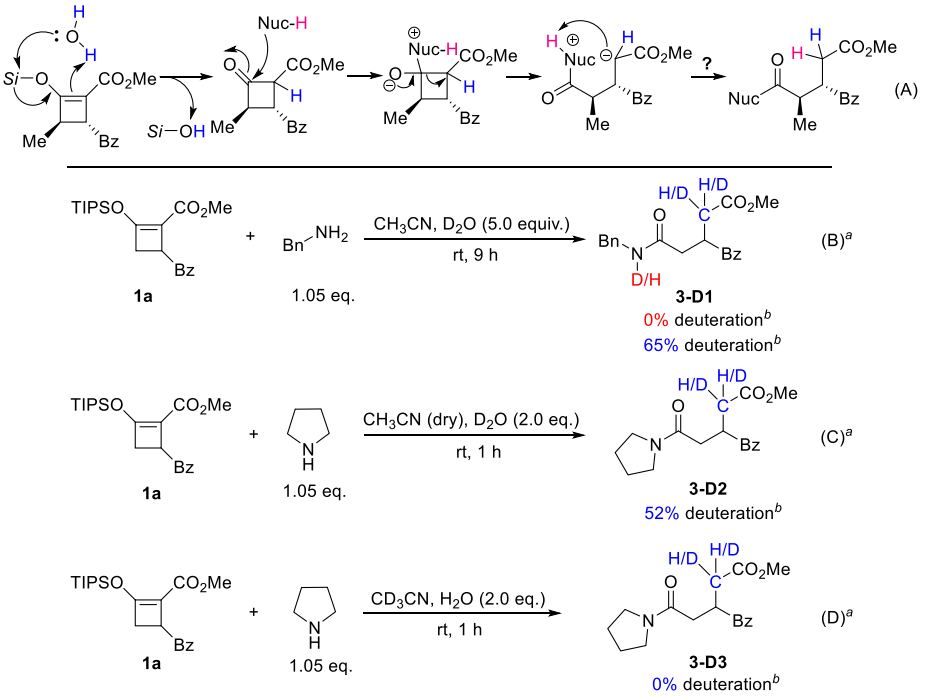
Scheme 8. Proposed Reaction Mechanism and Deuterium Incorporation Experiments[a]



[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv) and **2** (*n* equiv) in solvent (2.0 mL) at room temperature for the indicated time. Bz = benzoyl. [b]Percent of deuterium incorporation was determined from ^{1}H NMR spectra of purified **3-D1**, **3-D2**, and **3-D3** (see the Supporting Information).

8C), consistent with minimal intramolecular proton transfer from pyrrolidine. No deuterium exchange was observed when 2 equiv of H_2O was added into the system in deuterated acetonitrile, which suggests the complete absence of proton−deuterium exchange between acetonitrile and water under the reaction conditions (Scheme 8D). The major mode of proton transfer to the ring-opened ester enolate is from the nucleophile in an intramolecular transformation, rather than from water by intermolecular proton transfer.

CONCLUSIONS

In summary, we have achieved the ring-opening reactions of donor−acceptor 2-silyloxycyclobutene-1-carboxylates by various amine, alcohol, and thiol nucleophiles with good to excellent yields. Only 1 equiv of nucleophile is required with a stoichiometric amount of water when the nucleophile is an aliphatic amine. With less reactive nucleophiles, conversion of the less reactive donor−acceptor cyclobutenes to their corresponding β-keto esters facilitates their retro-Claisen reaction, and additional activation is achieved with the use of DMAP. The optical purity of the reactant donor−acceptor cyclobutene is fully retained in the retro-Claisen reaction products. Subsequent transformations of these 3-acylglutaric acid derivatives produce amido-diol, γ-aminobutyric acid (GABA), furan, thiophene and 1,5-dihydro-5-phenyl-2*H*-pyrrol-2-one products that suggest the enormous diversity of this methodology for the construction of new chemical libraries.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reactions were carried out in oven-dried (120 °C) glassware with magnetic stirring under an atmosphere of dry nitrogen. Tetrahydrofuran (THF), dichloromethane (DCM), chloroform, and toluene were purified using a JC-Meyer solvent purification system. All other solvents were purified and dried using standard methods. Thin-layer chromatography (TLC) was carried out using Dynamic Adsorbents precoated (0.25 mm, F254) silica gel plates. Column chromatography was performed on CombiFlash Rf200 and Rf+ purification systems using normal-phase disposable columns. Melting points were measured uncorrected on an Electro Thermo Mel-Temp DLX 104 device. High-resolution mass spectra (HRMS) were obtained on a Bruker MicroTOF-ESI mass spectrometer with an ESI resource using CsI or LTQ ESI positive-ion calibration solution as the standard. Accurate masses were reported for the molecular ions $[M + H]^+$. Enantioselectivities were determined by HPLC analysis at 25 °C using an Agilent 1260 Infinity HPLC System equipped with a G1311B quaternary pump, G1315D diode array detector, G1329B autosampler, G1316A thermostated column compartment, and G1170A valve drive. For instrument control and data processing, the Agilent OpenLAB CDS ChemStation Edition for LC & LC/MS Systems (Rev. C.01.07[26]) software was used. Chiralpak AD-H (0.46 mm × 250 mm), IA (0.46 mm × 250 mm), IC3 (0.46 mm × 250 mm), OJ-H (0.46 mm × 250 mm), and OD-H (0.46 mm × 250 mm) columns were obtained from Daicel Chiral Technologies. High-performance liquid chromatography (HPLC) analysis was conducted using an Agilent 1220 Infinity HPLC system with a Poroshell 120 EC-C18 column and water/acetonitrile as eluent. ^{1}H NMR spectra were recorded on a Bruker spectrometer (300 or 500 MHz) in $CDCl_3$ with residual $CHCl_3$ (δ 7.26 ppm) and H_2O (δ 1.56 ppm). Chemical shifts (δ values) are reported in ppm downfield from the internal standard tetramethylsilane (TMS, δ 0.00 ppm). Multiplicities are reported as s (singlet); br (broad singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets); ddd (doublet of doublets of doublets); dt (doublet of triplets); td (triplet of doublets); dq (doublet of quartets); m (multiplet); comp (composite of magnetically non-equivalent protons). The number of protons (n) for a given resonance is reported as nH. Coupling constants (J) are given in hertz (Hz). ^{13}C{^{1}H} NMR spectra were recorded in $CDCl_3$ on a Bruker spectrometer at 75 or 126 MHz with the central resonance for $CDCl_3$ of δ 77.16 ppm.

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Materials. Donor−acceptor cyclobutenes **1** were synthesized according to the published procedures.[16,20] Nucleophiles and other chemicals were purchased from commercial sources and used as received.

General Procedure for Retro-Claisen Ring-Opening Reaction of Racemic Donor−Acceptor Cyclobutene 1a with Nucleophile 2 (Table 3). To an oven-dried 8 mL screw-capped vial equipped with a magnetic stirring bar were added donor−acceptor cyclobutene **1a** (38.9 mg, 0.100 mmol, 1.00 equiv) and wet nitromethane (0.1% of water) (2.00 mL, 0.0500 M). To the stirring reaction solution nucleophile **2** (1.05 equiv) was then added in one portion (for a liquid nucleophile a microsyringe was used), and stirring was continued at room temperature for the specified time period as the reaction progress was monitored by TLC. After disappearance of **1a**, the reaction solution was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (using mixtures of hexane/ethyl acetate or dichloromethane/methanol required for elution) to afford product **3a**.

*Methyl 3-Benzoyl-5-(benzylamino)-5-oxopentanoate (**3aa**).* Hexane/ethyl acetate 3:2 (v/v) as eluent. 32.9 mg, 97% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.04 (d, 2H, J = 7.5 Hz), 7.59 (t, 1H, J = 7.5 Hz), 7.49 (t, 2H, J = 7.5 Hz), 7.34−7.25 (comp, 3H), 7.23−7.18 (comp, 2H), 6.08 (br, 1H), 4.48−4.39 (m, 1H), 4.42−4.32 (comp, 2H), 3.62 (s, 3H), 2.84 (dd, 1H, J = 16.5, 7.5 Hz), 2.72 (dd, 1H, J = 15.0, 7.5 Hz), 2.57 (dd, 1H, J = 16.5, 6.5 Hz), 2.42 (dd, 1H, J = 15.0, 6.5 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 201.8, 172.1, 170.2, 138.0, 135.8, 133.5, 128.9, 128.8, 128.8, 127.9, 127.6, 52.0, 43.8, 39.3, 38.0, 35.9 ppm. HRMS (ESI): m/z calcd for $C_{20}H_{22}NO_4$ [M + H]$^+$ 340.1543, found 340.1538.

*Methyl 3-Benzoyl-5-oxo-5-(pyrrolidin-1-yl)pentanoate (**3ab**).* Hexane/ethyl acetate 1:4 (v/v) as eluent. 29.4 mg, 97% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.02 (d, 2H, J = 7.5 Hz), 7.52 (t, 1H, J = 7.5 Hz), 7.43 (t, 2H, J = 7.5 Hz), 4.45−4.40 (m, 1H), 3.58 (s, 3H), 3.40−3.31 (comp, 4H), 2.80−2.72 (comp, 2H), 2.53 (dd, 1H, J = 16.5, 7.5 Hz), 2.46 (dd, 1H, J = 16.5, 6.5 Hz), 1.93−1.84 (comp, 2H), 1.82−1.75 (comp, 2H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 202.1, 172.1, 168.7, 136.0, 133.2, 128.7, 128.7, 51.8, 46.6, 45.8, 38.7, 36.6, 36.0, 26.1, 24.4 ppm. HRMS (ESI): m/z calcd for $C_{17}H_{22}NO_4$ [M + H]$^+$ 304.1543, found 304.1536.

*Methyl 3-Benzoyl-5-oxo-5-(piperidin-1-yl)pentanoate (**3ac**).* Hexane/ethyl acetate 2:1 (v/v) as eluent. 31.1 mg, 98% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.05 (d, 2H, J = 7.5 Hz), 7.55 (t, 1H, J = 7.5 Hz), 7.47 (t, 2H, J = 7.5 Hz), 4.47−4.41 (m, 1H), 3.61 (s, 3H), 3.53−3.41 (comp, 2H), 3.40−3.31 (comp, 2H), 2.89 (dd, 1H, J = 16.5, 7.5 Hz), 2.73 (dd, 1H, J = 16.5, 6.5 Hz), 2.60−2.46 (comp, 2H), 1.66−1.58 (comp, 2H), 1.57−1.51 (comp, 2H), 1.51−1.45 (comp, 2H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 202.2, 172.2, 168.6, 136.1, 133.2, 128.8, 128.8, 52.0, 46.7, 43.0, 39.0, 36.1, 35.3, 26.5, 25.6, 24.6 ppm. HRMS (ESI): m/z calcd for $C_{18}H_{24}NO_4$ [M + H]$^+$ 318.1700, found 318.1690.

*Methyl 3-Benzoyl-5-(cyclohexylamino)-5-oxopentanoate (**3ad**).* Hexane/ethyl acetate 3:2 (v/v) as eluent. 31.8 mg, 96% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.02 (d, 2H, J = 7.5 Hz), 7.56 (t, 1H, J = 7.5 Hz), 7.46 (t, 2H, J = 7.5 Hz), 5.46 (d, 1H, J = 6.5 Hz), 4.42−4.36 (m, 1H), 3.71−3.63 (m, 1H), 3.61 (s, 3H), 2.82 (dd, 1H, J = 16.5, 7.5 Hz), 2.62 (dd, 1H, J = 15.0, 7.5 Hz), 2.54 (dd, 1H, J = 16.5, 6.5 Hz), 2.33 (dd, 1H, J = 15.0, 6.5 Hz), 1.91−1.82 (m, 1H), 1.76−1.53 (comp, 4H), 1.38−1.17 (comp, 2H), 1.16−0.95 (comp, 3H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 202.0, 172.2, 169.2, 136.0, 133.4, 128.9, 128.8, 52.0, 48.5, 39.4, 38.5, 35.9, 33.2, 33.0, 25.6, 24.9, 24.9 ppm. HRMS (ESI): m/z calcd for $C_{19}H_{26}NO_4$ [M + H]$^+$ 332.1856, found 332.1848.

*Methyl 5-Amino-3-benzoyl-5-oxopentanoate (**3ae**).* DCM/MeOH 95:5 (v/v) as eluent. 23.2 mg, 93% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.01 (d, 2H, J = 7.5 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.47 (t, 2H, J = 7.5 Hz), 5.66 (br, 1H), 5.55 (br, 1H), 4.40−4.34 (m, 1H), 3.62 (s, 3H), 2.82 (dd, 1H, J = 16.5, 7.5 Hz), 2.73 (dd, 1H, J = 15.0, 7.5 Hz), 2.57 (dd, 1H, J = 16.5, 6.5 Hz), 2.42 (dd, 1H, J = 15.0, 6.5 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 201.7, 172.6, 172.1, 135.8, 133.5, 128.9, 128.8, 52.1, 39.2, 37.1, 35.9 ppm. HRMS (ESI): m/z calcd for $C_{13}H_{16}NO_4$ [M + H]$^+$ 250.1074, found 250.1067.

*Methyl 3-Benzoyl-5-(tert-butylamino)-5-oxopentanoate (**3af**).* Hexane/ethyl acetate 2:1 (v/v) as eluent. 28.1 mg, 92% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.03 (d, 2H, J = 7.5 Hz), 7.56 (t, 1H, J = 7.5 Hz), 7.47 (t, 2H, J = 7.5 Hz), 5.34 (br, 1H), 4.41−4.36 (m, 1H), 3.62 (s, 3H), 2.83 (dd, 1H, J = 16.5, 7.5 Hz), 2.62−2.48 (comp, 2H), 2.26 (dd, 1H, J = 15.0, 6.5 Hz), 1.26 (s, 9H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 172.2, 169.4, 136.0, 133.4, 128.9, 128.8, 52.0, 51.6, 39.4, 39.3, 35.9, 28.8 ppm. HRMS (ESI): m/z calcd for $C_{17}H_{24}NO_4$ [M + H]$^+$ 306.1700, found 306.1688.

*Methyl 5-[(2-[1H-Indol-3-yl]ethyl)amino]-3-benzoyl-5-oxopentanoate (**3ag**).* Hexane/ethyl acetate 1:2 (v/v) as eluent. 38.1 mg, 97% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.14 (s, 1H), 8.00 (d, 2H, J = 7.5 Hz), 7.61−7.51 (comp, 2H), 7.45 (t, 2H, J = 7.5 Hz), 7.35 (d, 1H, J = 8.0 Hz), 7.19 (t, 1H, J = 7.5 Hz), 7.11 (t, 1H, J = 7.5 Hz), 6.98 (s, 1H), 5.61 (br, 1H), 4.41−4.36 (m, 1H), 3.60 (s, 3H), 3.53 (q, 2H, J = 6.5 Hz), 2.89 (dt, 2H, J = 8.0, 6.5 Hz), 2.78 (dd, 1H, J = 16.5, 7.5 Hz), 2.58 (dd, 1H, J = 15.0, 7.5 Hz), 2.50 (dd, 1H, J = 16.5, 6.5 Hz), 2.26 (dd, 1H, J = 15.0, 6.5 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 201.8, 172.1, 170.1, 136.5, 135.9, 133.5, 128.9, 128.8, 127.4, 122.4, 122.3, 119.6, 118.8, 112.9, 111.4, 52.0, 39.9, 39.3, 38.2, 35.9, 25.3 ppm. HRMS (ESI): m/z calcd for $C_{23}H_{25}N_2O_4$ [M + H]$^+$ 393.1809, found 393.1799.

*Methyl 3-Benzoyl-5-[methoxy(methyl)amino]-5-oxopentanoate (**3ah**).* Hexane/ethyl acetate 1:1 (v/v) as eluent. 26.7 mg, 91% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.06 (d, 2H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.49 (t, 2H, J = 7.5 Hz), 4.45−4.39 (m, 1H), 3.70 (s, 3H), 3.64 (s, 3H), 3.16 (s, 3H), 2.99 (dd, 1H, J = 16.5, 7.5 Hz), 2.83 (dd, 1H, J = 15.0, 7.5 Hz), 2.70 (dd, 1H, J = 16.5, 6.5 Hz), 2.57 (dd, 1H, J = 15.0, 6.5 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 201.8, 172.0, 172.0, 135.8, 133.2, 128.7, 128.6, 61.3, 51.9, 38.3, 35.8, 34.1, 32.2 ppm. HRMS (ESI): m/z calcd for $C_{15}H_{20}NO_5$ [M + H]$^+$ 294.1336, found 294.1337.

*Methyl 3-Benzoyl-5-[(2-mercaptoethyl)amino]-5-oxopentanoate (**3ai**).* Hexane/ethyl acetate 2:3 (v/v) as eluent. 26.3 mg, 85% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.00 (d, 2H, J = 7.5 Hz), 7.56 (t, 1H, J = 7.5 Hz), 7.46 (t, 2H, J = 7.5 Hz), 6.21 (br, 1H), 4.40−4.34 (m, 1H), 3.60 (s, 3H), 3.37−3.29 (comp, 2H), 2.81 (dd, 1H, J = 16.5, 7.5 Hz), 2.68 (dd, 1H, J = 16.5, 6.5 Hz), 2.55−2.51 (comp, 3H), 2.40 (dd, 1H, J = 15.0, 6.5 Hz), 1.32 (t, 1H, J = 8.5 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 201.8, 172.0, 170.5, 135.8, 133.5, 128.9, 128.7, 52.0, 42.5, 39.3, 38.0, 35.9, 24.5 ppm. HRMS (ESI): m/z calcd for $C_{15}H_{20}NO_4S$ [M + H]$^+$ 310.1108, found 310.1112.

*Methyl 3-Benzoyl-5-([5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-5-yl]amino)-5-oxopentanoate (**3aj**).* DCM/MeOH 95:5 (v/v) as eluent. 31.9 mg, 81% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.01 (d, 2H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.48 (t, 2H, J = 7.5 Hz), 6.35 (br, 1H), 4.57 (t, 1H, J = 6.0 Hz), 4.39−4.34 (m, 1H), 3.88−3.69 (comp, 4H), 3.65 (s, 3H), 3.59 (d, 2H, J = 6.0 Hz), 2.86 (dd, 1H, J = 16.5, 7.5 Hz), 2.76 (dd, 1H, J = 15.0, 7.5 Hz), 2.59 (dd, 1H, J = 16.5, 6.5 Hz), 2.50 (dd, 1H, J = 15.0, 6.5 Hz), 1.42 (s, 3H), 1.41 (s, 3H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 201.4, 172.2, 171.9, 135.7, 133.6, 129.0, 128.8, 99.1, 64.5, 64.2, 64.1, 55.5, 52.1, 39.6, 38.6, 35.8, 27.9, 19.3 ppm. HRMS (ESI): m/z calcd for $C_{20}H_{28}NO_7$ [M + H]$^+$ 394.1860, found 394.1864.

*Methyl 3-Benzoyl-5-[benzyl(phenyl)amino]-5-oxopentanoate (**3ak**).* Hexane/ethyl acetate 2:1 (v/v) as eluent. 38.2 mg, 92% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.01 (d, 2H, J = 7.5 Hz), 7.56 (t, 1H, J = 7.5 Hz), 7.47 (t, 2H, J = 7.5 Hz), 7.35−7.28 (comp, 3H), 7.25−7.20 (comp, 3H), 7.15−7.09 (comp, 2H), 6.99−6.95 (comp, 2H), 4.88 (d, 1H, J = 14.5 Hz), 4.80 (d, 1H, J = 14.5 Hz), 4.50−4.44 (m, 1H), 3.58 (s, 3H), 2.71 (dd, 1H, J = 16.5, 7.5 Hz), 2.59 (dd, 1H, J = 15.0, 7.5 Hz), 2.44 (dd, 1H, J = 16.5, 6.5 Hz), 2.25 (dd, 1H, J = 15.0, 6.5 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 201.7, 172.0, 170.2, 141.8, 137.2, 135.8, 133.2, 129.7, 128.8, 128.7, 128.7, 128.5, 128.4, 128.2, 127.4, 53.2, 51.8, 39.2, 36.4, 35.7

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ppm. HRMS (ESI): m/z calcd for $C_{26}H_{26}NO_4$ $[M + H]^+$ 416.1856, found 416.1844.

*Methyl 5-(Adamantan-1-ylamino)-3-benzoyl-5-oxopentanoate (**3al**).* Hexane/ethyl acetate 2:1 (v/v) as eluent. 35.3 mg, 92% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.03 (d, 2H, J = 7.5 Hz), 7.56 (t, 1H, J = 7.5 Hz), 7.47 (t, 2H, J = 7.5 Hz), 5.20 (br, 1H), 4.40−4.34 (m, 1H), 3.62 (s, 3H), 2.84 (dd, 1H, J = 16.5, 7.5 Hz), 2.62−2.50 (comp, 2H), 2.25 (dd, 1H, J = 15.0, 6.5 Hz), 2.07−1.99 (br, 3H), 1.95−1.86 (br, 6H), 1.70−1.57 (br, 6H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 201.9, 172.2, 169.1, 136.0, 133.4, 128.9, 128.8, 52.3, 52.0, 41.7, 39.5, 39.3, 36.4, 35.8, 29.5 ppm. HRMS (ESI): m/z calcd for $C_{23}H_{30}NO_4$ $[M + H]^+$ 384.2169, found 384.2169.

*Methyl 3-Benzoyl-5-[(S)-3-mercapto-1-methoxy-1-oxopropan-2-yl]amino-5-oxopentanoate (**3am**).* Hexane/ethyl acetate 1:1 (v/v) as eluent. 31.9 mg, 87% yield. Colorless oil. ^{1}H NMR [mixture of diastereomers] ($CDCl_3$, 500 MHz): δ 8.01 (d, 2H, J = 7.5 Hz), 7.55 (t, 1H, J = 7.5 Hz), 7.46 (t, 2H, J = 7.5 Hz), 6.80−6.65 (m, 1H), 4.85−4.72 (m, 1H), 4.39−4.35 (m, 1H), 3.76−3.68 (comp, 3H), 3.63−3.59 (comp, 3H), 3.18−3.00 (comp, 2H), 2.87−2.75 (comp, 2H), 2.59−2.46 (comp, 2H) ppm. ^{13}C{^{1}H} NMR [mixture of diastereomers] ($CDCl_3$, 126 MHz): δ 201.7, 201.6, 201.4, 172.1, 172.1, 170.8, 170.7, 170.5, 170.5, 170.5, 135.8, 135.8, 133.5, 133.5, 128.9, 128.8, 53.0, 52.9, 52.1, 52.0, 51.9, 51.0, 40.7, 40.7, 40.6, 40.4, 39.2, 37.7, 37.6, 35.7 ppm. HRMS (ESI): m/z calcd for $C_{34}H_{40}N_2O_{12}S_2$ (dimer) $[M + H]^+$ 733.2095, found 733.2098.

*Methyl N^6-(3-Benzoyl-5-methoxy-5-oxopentanoyl)-L-lysinate (**3an**).* DCM/MeOH 90:10 (v/v) as eluent. 35.3 mg, 90% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.01 (d, 2H, J = 7.5 Hz), 7.55 (t, 1H, J = 7.5 Hz), 7.45 (t, 2H, J = 7.5 Hz), 5.88 (br, 1H), 4.41−4.35 (m, 1H), 3.69 (s, 3H), 3.67 (m, 1H), 3.60 (s, 3H), 3.40 (br, 2H), 3.16 (dd, 2H, J = 13.0, 6.5 Hz), 2.80 (dd, 1H, J = 16.5, 7.5 Hz), 2.63 (dd, 1H, J = 15.0, 7.5 Hz), 2.53 (dd, 1H, J = 16.5, 6.5 Hz), 2.34 (dd, 1H, J = 15.0, 6.5 Hz), 1.52−1.32 (comp, 6H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 201.9, 172.1, 170.2, 135.9, 133.4, 128.8, 128.7, 54.2, 52.1, 52.0, 39.4, 39.3, 38.2, 35.9, 34.3, 29.1, 22.9 ppm. HRMS (ESI): m/z calcd for $C_{20}H_{29}N_2O_6$ $[M + H]^+$ 393.2020, found 393.2022.

Procedure for the Synthesis of β-Keto Ester 4a (eq 1). To an oven-dried 8 mL screw-capped vial equipped with a magnetic stirring bar were sequentially added cyclobutene **1a** (194 mg, 0.500 mmol, 1.00 equiv), dry $CHCl_3$ (0.500 mL, 1.00 M), and trifluoroacetic acid (TFA, 570 mg, 5.00 mmol 10.0 equiv) under the flow of dry nitrogen. The reaction solution was stirred at room temperature for 1 h, which was then directly subjected to flash chromatography on silica gel using a mixture hexane/ethyl acetate 2:1 (v/v) as eluent to afford the β-keto ester product methyl *trans*-2-benzoyl-4-oxocyclobutane-1-carboxylate (**4a**) as a colorless oil (104.5 mg, 90% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.05 (d, 2H, J = 7.5 Hz), 7.62 (t, 1H, J = 7.5 Hz), 7.51 (t, 2H, J = 7.5 Hz), 4.66 (dt, 1H, J = 7.5, 2.0 Hz), 4.54 (dt, 1H, J = 8.0, 7.5 Hz), 3.79 (s, 3H), 3.58 (ddd, 1H, J = 18.0, 8.0, 2.0 Hz), 3.41 (ddd, 1H, J = 18.0, 8.0, 2.0 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 197.1, 195.6, 166.1, 134.9, 134.2, 129.1, 128.9, 66.5, 53.0, 50.1, 33.4 ppm. HRMS (ESI): m/z calcd for $C_{13}H_{13}O_4$ $[M + H]^+$ 233.0808, found 233.0809.

General Procedure for Retro-Claisen Ring-Opening Reaction of β-Keto Ester 4a with Nucleophile 2 (Scheme 3). To an oven-dried 8 mL screw-capped vial equipped with a magnetic stirring bar were added sequentially β-keto ester **4a** (23.2 mg, 0.100 mmol, 1.00 equiv), dry DCM (1.00 mL, 0.100 M), 4-dimethylaminopyridine (DMAP, 2.40 mg, 0.0200 mmol, 0.200 equiv), and nucleophile **2** (1.10 equiv) under the flow of dry nitrogen. The reaction solution was then stirred at room temperature under an atmosphere of dry nitrogen for the specified time as the reaction progress was monitored by TLC. After the completion, the reaction solution was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (using mixtures of hexane/ethyl acetate required for elution) to afford product **3a**.

*3-Benzoyl-5-methoxy-5-oxopentanoic Acid (**3ao**).* DCM/MeOH 95:5 (v/v) as eluent. 20.8 mg, 83% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.98 (d, 2H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.48 (t, 2H, J = 7.5 Hz), 4.31−4.25 (m, 1H), 3.63 (s, 3H), 2.95−2.74 (comp, 2H), 2.63−2.46 (comp, 2H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 200.8, 176.8, 172.0, 135.6, 133.6, 129.0, 128.7, 52.1, 38.9, 35.7, 35.6 ppm. HRMS (ESI): m/z calcd for $C_{13}H_{15}O_5$ $[M + H]^+$ 251.0914, found 251.0918.

*Dimethyl 3-Benzoylpentanedioate (**3ap**).* Hexane/ethyl acetate 3:1 (v/v) as eluent. 24.6 mg, 93% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.01 (d, 2H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.49 (t, 2H, J = 7.5 Hz), 4.35−4.29 (m, 1H), 3.64 (s, 6H), 2.85 (dd, 2H, J = 16.5, 7.5 Hz), 2.54 (dd, 2H, J = 16.5, 7.5 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 201.0, 172.0, 172.0, 135.8, 133.5, 128.9, 128.7, 52.1, 52.1, 38.9, 35.9, 35.9 ppm. HRMS (ESI): m/z calcd for $C_{14}H_{17}O_5$ $[M + H]^+$ 265.1071, found 265.1072.

*Methyl 3-Benzoyl-5-(benzylthio)-5-oxopentanoate (**3aq**).* Hexane/ethyl acetate 4:1 (v/v) as eluent. 33.9 mg, 95% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.01 (d 2H, J = 7.5 Hz,), 7.59 (t, 1H, J = 7.5 Hz), 7.49 (t, 2H, J = 7.5 Hz), 7.34−7.19 (comp, 5H), 4.44−4.38 (m, 1H), 4.18−4.03 (comp, 2H), 3.63 (s, 3H), 3.07 (dd, 1H, J = 16.0, 6.5 Hz), 2.87 (dd, 1H, J = 16.5, 7.5 Hz), 2.77 (dd, 1H, J = 16.0, 7.5 Hz), 2.54 (dd, 1H, J = 16.5, 6.5 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 200.5, 196.5, 171.9, 137.2, 135.6, 133.6, 129.0, 128.9, 128.8, 128.8, 127.5, 52.1, 44.9, 39.1, 35.5, 33.6 ppm. HRMS (ESI): m/z calcd for $C_{20}H_{21}O_4S$ $[M + H]^+$ 357.1155, found 357.1155.

*Methyl 3-Benzoyl-5-oxo-5-(phenylamino)pentanoate (**3ar**).* Hexane/ethyl acetate 2:1 (v/v) as eluent. 29.3 mg, 90% yield. Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.03 (d, 2H, J = 7.5 Hz), 7.79 (s, 1H), 7.57 (t, 1H, J = 7.5 Hz), 7.49−7.42 (comp, 4H), 7.26 (t, 2H, J = 7.5 Hz), 7.07 (t, 1H, J = 7.5 Hz), 4.49−4.44 (m, 1H), 3.62 (s, 3H), 2.89−2.83 (comp, 2H), 2.63−2.57 (comp, 2H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 201.8, 172.1, 168.8, 137.8, 135.7, 133.6, 129.0, 128.9, 128.8, 124.5, 120.0, 52.1, 39.4, 38.8, 35.9 ppm. HRMS (ESI): m/z calcd for $C_{19}H_{20}NO_4$ $[M + H]^+$ 326.1387, found 326.1394.

General Procedure for Retro-Claisen Ring-Opening Reaction of Chiral Donor−Acceptor Cyclobutene 1 with Nucleophile 2 (Tables 4 and 5, Scheme 5). To an oven-dried 8 mL screw-capped vial equipped with a magnetic stirring bar were added donor−acceptor cyclobutene **1** (0.100 mmol, 1.00 equiv) and wet nitromethane (0.1% of water) (2.00 mL, 0.0500 M). The stirring reaction solution nucleophile **2** (1.05 equiv) was then added in one portion (for a liquid nucleophile a microsyringe was used), and stirring was continued at room temperature for a certain time period as the reaction progress was monitored by TLC. After the disappearance of **1**, the reaction solution was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (using mixtures of hexane/ethyl acetate or dichloromethane/methanol required for elution) to afford chiral product **5**.

*Methyl (3S,4R)-3-Benzoyl-5-(benzylamino)-4-methyl-5-oxopentanoate (**5ba**).* Hexane/ethyl acetate 3:2 (v/v) as eluent. 34.6 mg, 98% yield. White solid, mp 119−120 °C. 98% ee [HPLC conditions: Chiralpak AD-H column, hexanes/*i*PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 12.9 min for minor isomer, t_R = 16.5 min for major isomer]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (d, 2H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.48 (t, 2H, J = 7.5 Hz), 7.36−7.24 (comp, 5H), 5.97 (br, 1H), 4.43 (d, 2H, J = 5.4 Hz), 4.27−4.19 (m, 1H), 3.55 (s, 3H), 2.89 (dd, 1H, J = 16.5, 9.9 Hz), 2.66−2.48 (comp, 2H), 1.08 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 202.9, 173.8, 172.3, 138.1, 137.8, 133.5, 128.9, 128.9, 128.8, 128.0, 127.8, 52.0, 44.5, 44.0, 43.9, 35.7, 16.9 ppm. HRMS (ESI): m/z calcd for $C_{21}H_{24}NO_4$ $[M + H]^+$ 354.1700, found 354.1703.

*Methyl (3S,4R)-3-Benzoyl-4-methyl-5-oxo-5-(pyrrolidin-1-yl)-pentanoate (**5bb**).* Hexane/ethyl acetate 1:4 (v/v) as eluent. 30.0 mg, 95% yield. Colorless oil. 98% ee [HPLC conditions: Chiralpak IA column, hexanes/*i*PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 42.7 min for minor isomer, t_R = 47.9 min for major isomer]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.10 (d, 2H, J = 7.5 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.48 (t, 2H, J = 7.5 Hz), 4.34−4.30 (m, 1H),

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3.56−3.38 (comp, 7H), 2.91−2.82 (comp, 2H), 2.58 (dd, 1H, J = 16.5, 3.5 Hz), 2.04−1.91 (comp, 2H), 1.91−1.83 (comp, 2H), 0.98 (d, 3H, J = 6.9 Hz) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 203.8, 172.8, 172.2, 138.4, 133.4, 128.8, 128.8, 51.8, 46.8, 46.0, 44.2, 41.3, 36.4, 26.2, 24.4, 16.5 ppm. HRMS (ESI): m/z calcd for $C_{18}H_{24}NO_4$ $[M + H]^+$ 318.1700, found 318.1702.

*Methyl (3S,4R)-3-Benzoyl-4-methyl-5-oxo-5-(piperidin-1-yl)-pentanoate (**5bc**).* Hexane/ethyl acetate 2:1 (v/v) as eluent. 32.1 mg, 97% yield. Colorless oil. 98% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 8.0 min for major isomer, t_R = 10.4 min for minor isomer]. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.09 (d, 2H, J = 7.5 Hz), 7.56 (t, 1H, J = 7.5 Hz), 7.47 (t, 2H, J = 7.5 Hz), 4.38−4.33 (m, 1H), 3.69−3.62 (m, 1H), 3.50 (s, 3H), 3.54−3.45 (comp, 2H), 3.44−3.37 (m, 1H), 3.04 (dq, 1H, J = 10.0, 6.9 Hz), 2.85 (dd, 1H, J = 16.5, 10.5 Hz), 2.56 (dd, 1H, J = 16.5, 3.5 Hz), 1.70−1.61 (comp, 2H), 1.60−1.50 (comp, 4H), 0.95 (d, 3H, J = 6.9 Hz) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 204.0, 172.6, 172.2, 138.4, 133.4, 128.8, 128.7, 51.8, 47.0, 44.2, 43.3, 38.7, 36.6, 27.0, 25.9, 24.7, 16.9 ppm. HRMS (ESI): m/z calcd for $C_{19}H_{26}NO_4$ $[M + H]^+$ 332.1856, found 332.1858.

*Methyl (3S,4R)-3-Benzoyl-5-(cyclohexylamino)-4-methyl-5-oxo-pentanoate (**5bd**).* Hexane/ethyl acetate 3:2 (v/v) as eluent. 32.5 mg, 94% yield. White solid, mp 138−139 °C. 99% ee [HPLC conditions: Chiralpak AD-H column, hexanes/*i*PrOH = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 15.8 min for major isomer, t_R = 19.8 min for minor isomer]. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.05 (d, 2H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.48 (t, 2H, J = 7.5 Hz), 5.64 (d, 1H, J = 8.1 Hz), 4.23−4.15 (m, 1H), 3.84−3.67 (m, 1H), 3.54 (s, 3H), 2.90 (dd, 1H, J = 16.5, 10.5 Hz), 2.59 (dd, 1H, J = 16.5, 3.5 Hz), 2.47 (dq, 1H, J = 10.0, 6.9 Hz), 1.98−1.55 (comp, 5H), 1.45−1.27 (comp, 2H), 1.23−1.07 (comp, 3H), 1.04 (d, 3H, J = 6.9 Hz) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 203.1, 172.8, 172.3, 137.9, 133.5, 128.8, 128.7, 51.9, 48.3, 44.4, 44.1, 35.6, 33.3, 33.0, 25.6, 24.9, 16.8 ppm. HRMS (ESI): m/z calcd for $C_{20}H_{28}NO_4$ $[M + H]^+$ 346.2013, found 346.2018.

*Methyl (3S,4R)-5-Amino-3-benzoyl-4-methyl-5-oxopentanoate (**5be**).* DCM/MeOH 95:5 (v/v) as eluent. 24.5 mg, 93% yield. Colorless oil. 98% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 15.9 min for major isomer, t_R = 21.5 min for minor isomer]. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.06 (d, 2H, J = 7.5 Hz), 7.59 (t, 1H, J = 7.5 Hz), 7.49 (t, 2H, J = 7.5 Hz), 5.87 (br, 1H), 5.67 (br, 1H), 4.21−4.16 (m, 1H), 3.55 (s, 3H), 2.94 (dd, 1H, J = 16.5, 10.5 Hz), 2.71−2.62 (comp, 2H), 1.09 (d, 3H, J = 6.9 Hz) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 203.0, 176.5, 172.3, 137.8, 133.6, 128.9, 128.8, 52.0, 44.3, 43.1, 35.7, 16.9 ppm. HRMS (ESI): m/z calcd for $C_{14}H_{18}NO_4$ $[M + H]^+$ 264.1230, found 264.1234.

*Methyl (3S,4R)-3-Benzoyl-5-(tert-butylamino)-4-methyl-5-oxo-pentanoate (**5bf**).* Hexane/ethyl acetate 2:1 (v/v) as eluent. 29.1 mg, 91% yield. White solid, mp 119−120 °C. 99% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 97:3, flow rate = 0.7 mL/min, wavelength = 254 nm, t_R = 17.5 min for major isomer, t_R = 20.4 min for minor isomer]. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.05 (d, 2H, J = 7.5 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.48 (t, 2H, J = 7.5 Hz), 5.51 (br, 1H), 4.19−4.15 (m, 1H), 3.54 (s, 3H), 2.91 (dd, 1H, J = 16.5, 10.5 Hz), 2.60 (dd, 1H, J = 16.5, 3.5 Hz), 2.40 (dq, 1H, J = 10.0, 6.9 Hz), 1.34 (s, 9H), 1.03 (d, 3H, J = 6.9 Hz) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 203.1, 173.2, 172.4, 138.0, 133.5, 128.9, 128.7, 51.9, 51.6, 44.6, 44.5, 35.6, 28.9, 16.9 ppm. HRMS (ESI): m/z calcd for $C_{18}H_{26}NO_4$ $[M + H]^+$ 320.1856, found 320.1862.

*Methyl (3S,4R)-5-([2-(1H-Indol-3-yl)ethyl]amino)-3-benzoyl-4-methyl-5-oxopentanoate (**5bg**).* Hexane/ethyl acetate 1:3 (v/v) as eluent. 39.0 mg, 96% yield. Colorless oil. 99% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 60:40, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 7.9 min for major isomer, t_R = 13.8 min for minor isomer]. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.21 (s, 1H), 8.02 (d, 2H, J = 7.5 Hz), 7.61 (d, 1H, J = 7.5 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.46 (t, 2H, J = 7.5 Hz), 7.38 (d, 1H, J = 7.5 Hz), 7.21 (t, 1H, J = 7.5 Hz), 7.13 (t, 1H, J = 7.5 Hz), 7.03 (s, 1H), 5.76 (br, 1H), 4.24−4.16 (m, 1H), 3.65 (dd, 1H, J = 12.5, 6.0 Hz), 3.57 (dd, 1H, J = 12.5, 6.0 Hz), 3.52 (s, 3H), 2.97 (dt, 2H, J = 8.0, 6.0 Hz), 2.83 (dd, 1H, J = 16.5, 10.5 Hz), 2.53 (dd, 1H, J = 16.5, 3.5 Hz), 2.45−2.34 (m, 1H), 0.99 (d, 3H, J = 6.9 Hz) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 203.1, 173.9, 172.3, 137.9, 136.6, 133.5, 128.8, 128.7, 127.4, 122.4, 122.3, 119.7, 118.8, 112.8, 111.5, 51.9, 44.3, 44.2, 39.7, 35.8, 25.5, 16.8 ppm. HRMS (ESI): m/z calcd for $C_{24}H_{27}N_2O_4$ $[M + H]^+$ 407.1965, found 407.1969.

*Methyl (3S,4R)-3-Benzoyl-5-[methoxy(methyl)amino]-4-methyl-5-oxopentanoate (**5bh**).* Hexane/ethyl acetate 1:1 (v/v) as eluent. 28.3 mg, 92% yield. Colorless oil. 98% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 10.4 min for major isomer, t_R = 12.8 min for minor isomer]. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.08 (d, 2H, J = 7.5 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.48 (t, 2H, J = 7.5 Hz), 4.30−4.25 (m, 1H), 3.67 (s, 3H), 3.53 (s, 3H), 3.24−3.14 (comp, 1H), 3.18 (s, 3H), 2.95 (dd, 1H, J = 16.5, 10.5 Hz), 2.55 (dd, 1H, J = 16.5, 3.5 Hz), 1.00 (d, 3H, J = 6.9 Hz) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 203.3, 175.4, 172.4, 138.3, 133.3, 128.8, 128.8, 61.8, 51.8, 43.8, 38.5, 36.1, 32.4, 16.5 ppm. HRMS (ESI): m/z calcd for $C_{16}H_{22}NO_5$ $[M + H]^+$ 308.1492, found 308.1498.

*Methyl (3S,4R)-3-Benzoyl-5-[(2-mercaptoethyl)amino]-4-methyl-5-oxopentanoate (**5bi**).* Hexane/ethyl acetate 2:3 (v/v) as eluent. 27.5 mg, 85% yield. Colorless oil. 99% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 12.0 min for major isomer, t_R = 15.3 min for minor isomer]. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.05 (d, 2H, J = 7.5 Hz), 7.59 (t, 1H, J = 7.5 Hz), 7.50 (t, 2H, J = 7.5 Hz), 6.11 (br, 1H), 4.22−4.18 (m, 1H), 3.56 (s, 3H), 3.51−3.44 (comp, 1H), 3.42−3.35 (comp, 1H), 2.92 (dd, 1H, J = 16.5, 10.0 Hz), 2.72−2.55 (comp, 4H), 1.38 (t, 1H, J = 8.5 Hz), 1.09 (d, 3H, J = 6.9 Hz) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 202.8, 174.0, 172.3, 137.7, 133.6, 128.9, 128.8, 52.0, 44.5, 43.8, 42.4, 35.5, 24.7, 16.8 ppm. HRMS (ESI): m/z calcd for $C_{16}H_{22}NO_4S$ $[M + H]^+$ 324.1264, found 324.1272.

*Methyl (3S,4R)-3-Benzoyl-5-([5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-5-yl]amino)-4-methyl-5-oxopentanoate (**5bj**).* DCM/MeOH 95:5 (v/v) as eluent. 33.4 mg, 82%. White solid, mp 109−110 °C. 99% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 12.5 min for major isomer, t_R = 16.5 min for minor isomer]. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.05 (d, 2H, J = 7.5 Hz), 7.59 (t, 1H, J = 7.5 Hz), 7.49 (t, 2H, J = 7.5 Hz), 6.47 (br, 1H), 4.22−4.18 (m, 1H), 3.93−3.80 (comp, 4H), 3.70−3.61 (comp, 2H), 3.57 (s, 3H), 2.94 (dd, 1H, J = 16.5, 10.0 Hz), 2.69 (comp, 2H), 1.44 (s, 3H), 1.42 (s, 3H), 1.11 (d, 3H, J = 6.9 Hz) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 202.6, 175.6, 172.4, 137.6, 133.6, 128.9, 128.8, 99.1, 64.2, 64.2, 64.1, 55.5, 52.0, 44.5, 43.9, 35.5, 27.9, 19.4, 16.6 ppm. HRMS (ESI): m/z calcd for $C_{21}H_{30}NO_7$ $[M + H]^+$ 408.2017, found 408.2024.

*Methyl (3S,4R)-5-(Adamantan-1-ylamino)-3-benzoyl-4-methyl-5-oxopentanoate (**5bl**).* Hexane/ethyl acetate 2:1 (v/v) as eluent. 35.8 mg, 90% yield. Colorless oil. 98% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 97:3, flow rate = 0.5 mL/min, wavelength = 254 nm, t_R = 26.2 min for major isomer, t_R = 32.0 min for minor isomer]. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.04 (d, 2H, J = 7.5 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.48 (t, 2H, J = 7.5 Hz), 5.33 (br, 1H), 4.16−4.12 (m, 1H), 3.54 (s, 3H), 2.91 (dd, 1H, J = 16.5, 10.0 Hz), 2.61 (dd, 1H, J = 16.5, 3.5 Hz), 2.39 (dq, 1H, J = 10.0, 6.9 Hz), 2.11−2.04 (br, 3H), 2.03−1.94 (br, 6H), 1.73−1.60 (br, 6H), 1.02 (d, 3H, J = 6.9 Hz) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ 203.2, 172.9, 172.4, 138.0, 133.4, 128.9, 128.7, 52.3, 51.9, 44.7, 44.5, 41.7, 36.5, 35.5, 29.6, 17.0 ppm. HRMS (ESI): m/z calcd for $C_{24}H_{32}NO_4$ $[M + H]^+$ 398.2326, found 398.2335.

*Methyl (3S,4R)-3-Benzoyl-5-([(S)-3-mercapto-1-methoxy-1-oxo-propan-2-yl]amino)-4-methyl-5-oxopentanoate (**5bm**).* Hexane/ethyl acetate 1:1 (v/v) as eluent. 32.8 mg, 86% yield. mp 159−160 °C. 98% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R =

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20.4 min for major isomer, t_R = 31.9 min for minor isomer]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.05 (d, 2H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.48 (t, 2H, J = 7.5 Hz), 6.75 (d, 1H, J = 7.5 Hz), 4.84−4.78 (m, 1H), 4.23−4.19 (m, 1H), 3.77 (s, 3H), 3.54 (s, 3H), 3.22 (d, 2H, J = 5.5 Hz), 2.97 (dd, 1H, J = 16.5, 10.0 Hz), 2.75−2.63 (comp, 2H), 1.70 (br, 1H, 1.09 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 202.7, 174.1, 172.4, 170.8, 137.8, 133.5, 128.9, 128.8, 53.0, 52.0, 51.9, 44.3, 43.6, 40.6, 35.7, 16.7 ppm. HRMS (ESI): m/z calcd for $C_{36}H_{44}N_2O_{12}S_2$ (dimer) [M + H]$^+$ 761.2408, found 761.2430.

*Diethyl [(2R,3S)-3-Benzoyl-5-methoxy-2-methyl-5-oxopentanoyl]-L-glutamate (**5bs**).* Hexane/ethyl acetate 1:1 (v/v) as eluent. 37.3 mg, 83% yield. Colorless oil. 98% ee [HPLC conditions: Chiralpak AD-H column, hexanes/*i*PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 16.8 min for major isomer, t_R = 20.4 min for minor isomer]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.06 (d, 2H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.48 (t, 2H, J = 7.5 Hz), 6.46 (d, 1H, J = 7.5 Hz), 4.56−4.52 (m, 1H), 4.23−4.14 (comp, 5H), 3.55 (s, 3H), 2.93 (dd, 1H, J = 16.5, 10.0 Hz), 2.66−2.56 (comp, 2H), 2.50−2.36 (comp, 2H), 2.25−2.17 (m, 1H), 2.07−1.99 (m, 1H), 1.28 (t, 6H, J = 7.5 Hz), 1.08 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 202.7, 174.0, 173.1, 172.3, 171.7, 137.8, 133.5, 128.9, 128.7, 61.8, 61.0, 52.0, 51.9, 44.2, 43.8, 35.5, 30.5, 27.1, 16.8, 14.3, 14.3 ppm. HRMS (ESI): m/z calcd for $C_{23}H_{32}NO_8$ [M + H]$^+$ 450.2122, found 450.2130.

*Methyl (3S,4R)-5-(Benzylamino)-3-(4-methoxybenzoyl)-4-methyl-5-oxopentanoate (**5ca**).* Hexane/ethyl acetate 1:1 (v/v) as eluent. 37.2 mg, 97% yield. White solid, mp 136−137 °C. 98% ee [HPLC conditions: Chiralpak IA column, hexanes/*i*PrOH = 60:40, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 8.5 min for minor isomer, t_R = 17.6 min for major isomer]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.02 (d, 2H, J = 9.0 Hz), 7.35−7.31 (comp, 2H), 7.30−7.25 (comp, 3H), 6.94 (d, 2H, J = 9.0 Hz), 6.23 (t, 1H, J = 5.4 Hz), 4.50−4.39 (comp, 2H), 4.22−4.17 (m, 1H), 3.87 (s, 3H), 3.53 (s, 3H), 2.87 (dd, 1H, J = 16.5, 10.0 Hz), 2.64−2.52 (comp, 2H), 1.07 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 201.3, 174.1, 172.3, 164.0, 138.2, 131.2, 130.8, 128.9, 127.9, 127.7, 114.0, 55.6, 51.9, 44.1, 44.0, 43.8, 35.9, 16.9 ppm. HRMS (ESI): m/z calcd for $C_{22}H_{26}NO_5$ [M + H]$^+$ 384.1805, found 384.1807.

*Methyl (3S,4R)-5-(Benzylamino)-4-methyl-3-(4-methylbenzoyl)-5-oxopentanoate (**5da**).* Hexane/ethyl acetate 3:2 (v/v) as eluent. 35.3 mg, 96% yield. White solid, mp 113−114 °C. 99% ee [HPLC conditions: Chiralpak OJ-H column, hexanes/*i*PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 22.4 min for major isomer, t_R = 29.7 min for minor isomer]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.93 (d, 2H, J = 8.5 Hz), 7.37−7.24 (comp, 7H), 6.15 (t, 1H, J = 5.4 Hz), 4.43 (d, 2H, J = 5.7 Hz), 4.25−4.17 (m, 1H), 3.53 (s, 3H), 2.88 (dd, 1H, J = 16.5, 10.0 Hz), 2.66−2.53 (comp, 2H), 2.41 (s, 3H), 1.08 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 202.5, 173.9, 172.3, 144.5, 138.2, 135.3, 129.6, 128.9, 128.9, 127.9, 127.7, 51.9, 44.3, 44.0, 43.8, 35.8, 21.8, 16.9 ppm. HRMS (ESI): m/z calcd for $C_{22}H_{26}NO_4$ [M + H]$^+$ 368.1856, found 368.1859.

*Methyl (3S,4R)-5-(Benzylamino)-4-methyl-5-oxo-3-(thiophene-2-carbonyl)pentanoate (**5ea**).* Hexane/ethyl acetate 3:2 (v/v) as eluent. 34.1 mg, 95% yield. White solid, mp 113−114 °C. 97% ee [HPLC conditions: Chiralpak IA column, hexanes/*i*PrOH = 60:40, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 6.2 min for minor isomer, t_R = 9.9 min for major isomer]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90 (d, 1H, J = 3.5 Hz), 7.69 (d, 1H, J = 5.0 Hz), 7.37−7.32 (comp, 2H), 7.31−7.26 (comp, 3H), 7.17 (dd, 1H, J = 5.0, 3.5 Hz), 6.04 (br, 1H), 4.51−4.37 (comp, 2H), 4.03−4.00 (m, 1H), 3.57 (s, 3H), 2.87 (dd, 1H, J = 16.5, 10.0 Hz), 2.64−2.56 (comp, 2H), 1.14 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 195.0, 173.8, 172.1, 145.3, 138.1, 135.0, 133.4, 129.0, 128.6, 128.0, 127.8, 52.0, 46.6, 44.0, 43.9, 35.7, 16.9 ppm. HRMS (ESI): m/z calcd for $C_{19}H_{22}NO_4S$ [M + H]$^+$ 360.1264, found 360.1272.

*Methyl (3S,4R)-5-(Benzylamino)-3-(4-bromobenzoyl)-4-methyl-5-oxopentanoate (**5fa**).* Hexane/ethyl acetate 3:2 (v/v) as eluent. 35.7 mg, 92% yield. White solid, mp 123−124 °C. 96% ee [HPLC conditions: Chiralpak AD-H column, hexanes/*i*PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 13.5 min for minor isomer, t_R = 20.3 min for major isomer]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.97 (d, 2H, J = 8.5 Hz), 7.44 (d, 2H, J = 8.5 Hz), 7.38−7.23 (comp, 5H), 6.11 (br, 1H), 4.42 (d, 2H, J = 5.5 Hz), 4.21−4.16 (m, 1H), 3.54 (s, 3H), 2.88 (dd,1H, J = 16.5, 10.0 Hz), 2.60 (dd,1H, J = 16.5, 3.5 Hz), 2.53 (dq, 1H, J = 10.0, 6.9 Hz), 1.05 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 202.0, 173.7, 172.2, 140.1, 138.0, 136.2, 130.2, 129.2, 128.9, 127.9, 127.8, 52.0, 44.2, 44.1, 43.8, 35.9, 16.8 ppm. HRMS (ESI): m/z calcd for $C_{21}H_{23}ClNO_4$ [M + H]$^+$ 388.1310, found 388.1312.

*Methyl (3S,4R)-5-(Benzylamino)-3-(4-bromobenzoyl)-4-methyl-5-oxopentanoate (**5ga**).* Hexane/ethyl acetate 3:2 (v/v) as eluent. 38.0 mg, 88% yield. White solid, mp 126−127 °C. 97% ee [HPLC conditions: Chiralpak AD-H column, hexanes/*i*PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 14.1 min for minor isomer, t_R = 20.7 min for major isomer]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.90 (d, 2H, J = 8.5 Hz), 7.62 (d, 2H, J = 8.5 Hz), 7.39−7.22 (comp, 5H), 6.07 (t, 1H, J = 5.4 Hz), 4.49−4.36 (comp, 2H), 4.22−4.15 (m, 1H), 3.55 (s, 3H), 2.90 (dd, 1H, J = 16.5, 10.0 Hz), 2.60 (dd, 1H, J = 16.5, 3.5 Hz), 2.53 (dq, 1H, J = 10.0, 6.9 Hz), 1.06 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ δ 202.2, 173.7, 172.2, 138.0, 136.7, 132.2, 130.3, 128.9, 128.9, 127.9, 127.8, 52.0, 44.2, 44.1, 43.8, 35.9, 16.8 ppm. HRMS (ESI): m/z calcd for $C_{21}H_{23}BrNO_4$ [M + H]$^+$ 432.0805, found 432.0808.

*Methyl (3S,4R)-5-(Benzylamino)-3-(4-cyanobenzoyl)-4-methyl-5-oxopentanoate (**5ha**).* Hexane/ethyl acetate 3:2 (v/v) as eluent. 34.8 mg, 92% yield. Colorless oil. 97% ee [HPLC conditions: Chiralpak AD-H column, hexanes/*i*PrOH = 70:30, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 6.8 min for minor isomer, t_R = 8.6 min for major isomer]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.14 (d, 2H, J = 8.5 Hz), 7.78 (d, 2H, J = 8.5 Hz), 7.37−7.28 (comp, 3H), 7.27−7.24 (comp, 2H), 5.91 (br, 1H), 4.43 (d, 2H, J = 6.0 Hz), 4.25−4.20 (m, 1H), 3.56 (s, 3H), 2.94 (dd, 1H, J = 16.5, 10.0 Hz), 2.64 (dd, 1H, J = 16.5, 3.5 Hz), 2.51 (dq, 1H, J = 10.0, 6.9 Hz), 1.07 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 202.1, 173.3, 172.3, 141.1, 137.9, 132.7, 129.1, 129.0, 128.0, 127.9, 118.1, 116.6, 52.1, 44.4, 44.3, 43.9, 36.1, 16.8 ppm. HRMS (ESI): m/z calcd for $C_{22}H_{23}N_2O_4$ [M + H]$^+$ 379.1652, found 379.1657.

*4-Methoxybenzyl (3S,4R)-3-Benzoyl-5-(benzylamino)-4-methyl-5-oxopentanoate (**5ia**).* Hexane/ethyl acetate 3:2 (v/v) as eluent. 43.7 mg, 95% yield. Colorless oil. 99% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 70:30, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 7.8 min for minor isomer, t_R = 13.8 min for major isomer]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.00 (d, 2H, J = 7.5 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.45 (t, 2H, J = 7.5 Hz), 7.34−7.30 (comp, 2H), 7.29−7.23 (comp, 3H), 7.14 (d, 2H, J = 8.5 Hz), 6.81 (d, 2H, J = 8.5 Hz), 6.04 (t, 1H, J = 5.5 Hz), 4.92 (d, 1H, J = 12.0 Hz), 4.87 (d, 1H, J = 12.0 Hz), 4.43 (dd, 1H, J = 15.0, 5.5 Hz), 4.37 (dd, 1H, J = 15.0, 5.5 Hz), 4.24−4.22 (m, 1H), 3.79 (s, 3H), 2.93 (dd, 1H, J = 16.5, 10.0 Hz), 2.63 (dd, 1H, J = 16.5, 3.5 Hz), 2.56 (dq, 1H, J = 10.0, 6.9 Hz), 1.07 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 202.8, 173.8, 171.6, 159.7, 138.1, 137.8, 133.5, 130.3, 128.9, 128.8, 128.8, 127.9, 127.7, 127.7, 114.0, 66.6, 55.4, 44.3, 44.0, 43.8, 36.0, 16.9 ppm. HRMS (ESI): m/z calcd for $C_{28}H_{30}NO_5$ [M + H]$^+$ 460.2118, found 460.2126.

*Methyl (3S,4R)-3-(4-Bromobenzoyl)-4-methyl-5-oxo-5-(piperidin-1-yl)pentanoate (**5gc**).* Hexane/ethyl acetate 2:1 (v/v) as eluent. 39.4 mg, 96% yield. White solid, mp 109−110 °C. 98% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 7.6 min for major isomer, t_R = 9.7 min for minor isomer]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.97 (d, 2H, J = 8.7 Hz), 7.62 (d, 2H, J = 8.7 Hz), 4.34−4.26 (m, 1H), 3.72−3.59 (m, 1H), 3.52 (s, 3H), 3.55−3.35 (comp, 3H), 3.00 (dq, 1H, J = 10.0, 6.9 Hz), 2.85 (dd, 1H, J = 16.5, 10.0 Hz), 2.57 (dd, 1H, J = 16.5, 3.5 Hz), 1.72−1.62 (comp, 2H), 1.62−1.50 (comp, 4H), 0.94 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 203.3, 172.3, 172.3, 137.2, 132.1, 130.3, 128.7, 51.9, 47.0, 44.1, 43.3, 38.9, 36.7, 27.0, 25.9, 24.7, 16.9 ppm. HRMS (ESI): m/z calcd for $C_{19}H_{25}BrNO_4$ [M + H]$^+$ 410.0961, found 410.0972.

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*Methyl (3S,4R)-3-(4-Cyanobenzoyl)-4-methyl-5-oxo-5-(piperidin-1-yl)pentanoate (**5hc**).* Hexane/ethyl acetate 2:1 (v/v) as eluent. 33.5 mg, 94% yield. Colorless oil. 98% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 6.8 min for minor isomer, t_R = 10.3 min for major isomer]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.19 (d, 2H, J = 8.7 Hz), 7.79 (d, 2H, J = 8.7 Hz), 4.36−4.28 (m, 1H), 3.71−3.57 (m, 1H), 3.53 (s, 3H), 3.52−3.35 (comp, 3H), 3.00 (dq, 1H, J = 10.0, 6.9 Hz), 2.88 (dd, 1H, J = 16.5, 10.0 Hz), 2.61 (dd, 1H, J = 16.5, 3.5 Hz), 1.75−1.63 (comp, 2H), 1.63−1.50 (comp, 4H), 0.94 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 203.3, 172.4, 172.0, 141.6, 132.7, 129.2, 118.2, 116.5, 52.0, 47.0, 44.3, 43.4, 39.0, 36.8, 27.0, 25.9, 24.7, 16.8 ppm. HRMS (ESI): m/z calcd for $C_{20}H_{25}N_2O_4$ [M + H]$^+$ 357.1809, found 357.1821.

*Methyl (3S,4R)-3-Benzoyl-4-(benzylcarbamoyl)hexanoate (**5ja**).* Hexane/ethyl acetate 3:2 (v/v) as eluent. 33.8 mg, 92% yield. White solid, mp 110−111 °C. 90% ee [HPLC conditions: Chiralpak OJ-H column, hexanes/*i*PrOH = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 8.0 min for minor isomer, t_R = 11.4 min for major isomer]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.03 (d, 2H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.48 (t, 2H, J = 7.5 Hz), 7.39−7.26 (comp, 5H), 6.05 (br, 1H), 4.51 (d, 1H, J = 15.0, 5.5 Hz), 4.43 (d, 1H, J = 15.0, 5.5 Hz), 4.25−4.17 (m, 1H), 3.54 (s, 3H), 2.90 (dd, 1H, J = 16.5, 10.0 Hz), 2.60 (dd, 1H, J = 16.5, 3.5 Hz), 2.36 (ddd, 1H, J = 10.0, 10.0, 3.5 Hz), 1.74−1.59 (m, 1H), 1.36−1.23 (m, 1H), 0.80 (t, 3H, J = 7.2 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 202.9, 172.9, 172.3, 138.1, 137.7, 133.5, 128.9, 128.9, 128.7, 128.1, 127.8, 51.9, 51.8, 44.0, 43.9, 35.6, 24.7, 12.4 ppm. HRMS (ESI): m/z calcd for $C_{22}H_{26}NO_4$ [M + H]$^+$ 368.1856, found 368.1865.

*Methyl (3S,4R)-3-Benzoyl-4-(piperidine-1-carbonyl)hexanoate (**5jc**).* Hexane/ethyl acetate 2:1 (v/v) as eluent. 32.5 mg, 94% yield. White solid, mp 109−110 °C. 90% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 7.7 min for major isomer, t_R = 15.7 min for minor isomer]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.10 (d, 2H, J = 7.5 Hz), 7.59 (t, 1H, J = 7.5 Hz), 7.49 (t, 2H, J = 7.5 Hz), 4.34−4.26 (m, 1H), 3.72−3.60 (comp, 2H), 3.58−3.50 (comp, 2H), 3.50 (s, 3H), 3.03 (ddd, 1H, J = 10.0, 10.0, 3.5 Hz), 2.89 (dd, 1H, J = 16.5, 10.0 Hz), 2.52 (dd, 1H, J = 16.5, 3.5 Hz), 1.72−1.52 (comp, 7H), 1.34−1.21 (m, 1H), 0.73 (t, 3H, J = 7.2 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 203.9, 172.2, 171.7, 138.2, 133.4, 128.8, 128.8, 51.8, 47.3, 45.0, 44.2, 43.3, 36.4, 27.0, 26.1, 25.3, 24.7, 12.1 ppm. HRMS (ESI): m/z calcd for $C_{20}H_{28}NO_4$ [M + H]$^+$ 346.2013, found 346.2023.

*Methyl (3S,4R)-3-Benzoyl-4-(cyclohexylcarbamoyl)hexanoate (**5jd**).* Hexane/ethyl acetate 3:2 (v/v) as eluent. 34.1 mg, 95% yield. White solid, mp 134−135 °C. 90% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 5.6 min for major isomer, t_R = 6.6 min for minor isomer]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.06 (d, 2H, J = 7.5 Hz), 7.59 (t, 1H, J = 7.5 Hz), 7.49 (t, 2H, J = 7.5 Hz), 5.66 (d, 1H, J = 8.0 Hz), 4.21−4.16 (m, 1H), 3.90−3.77 (m, 1H), 3.53 (s, 3H), 2.91 (dd, 1H, J = 16.5, 10.0 Hz), 2.59 (dd, 1H, J = 16.5, 3.5 Hz), 2.25 (ddd, 1H, J = 10.0, 10.0, 3.5 Hz), 1.98−1.86 (comp, 2H), 1.78−1.67 (comp, 2H), 1.67−1.56 (comp, 2H), 1.45−1.31 (comp, 2H), 1.29−1.08 (comp, 4H), 0.79 (t, 3H, J = 7.2 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 203.2, 172.3, 171.8, 137.9, 133.5, 128.9, 128.7, 52.1, 51.9, 48.4, 43.9, 35.6, 33.4, 33.3, 25.6, 24.9, 24.6, 12.3 ppm. HRMS (ESI): m/z calcd for $C_{21}H_{30}NO_4$ [M + H]$^+$ 360.2169, found 360.2178.

*Methyl (3S,4R)-3-Benzoyl-4-(tert-butylcarbamoyl)hexanoate (**5jf**).* Hexane/ethyl acetate 2:1 (v/v) as eluent. 30.0 mg, 90% yield. White solid, mp 120−121 °C. 90% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 4.7 min for major isomer, t_R = 6.4 min for minor isomer]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (d, 2H, J = 7.5 Hz), 7.56 (d, 1H, J = 7.5 Hz), 7.47 (t, 2H, J = 7.5 Hz), 5.50 (br, 1H), 4.18−4.11 (m, 1H), 3.53 (s, 3H), 2.90 (dd, 1H, J = 16.5, 10.0 Hz), 2.58 (dd, 1H, J = 16.5, 3.5 Hz), 2.16 (ddd, 1H, J = 10.0, 10.0, 3.5 Hz), 1.64−1.51 (m, 1H), 1.36 (s, 9H), 1.27−1.15 (m, 1H), 0.79 (t, 3H, J = 7.2 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 203.2, 172.4, 172.2, 137.9, 133.5, 128.9, 128.7, 52.5, 51.9, 51.9, 44.0, 35.6, 28.9, 24.7, 12.3 ppm. HRMS (ESI): m/z calcd for $C_{19}H_{28}NO_4$ [M + H]$^+$ 334.2013, found 334.2024.

Procedure for the Synthesis of β-Keto Ester 4b. To an oven-dried 8 mL screw-capped vial equipped with a magnetic stirring bar were sequentially added cyclobutene **1b** (201 mg, 0.500 mmol, 1.00 equiv), dry $CHCl_3$ (0.500 mL, 1.00 M), and trifluoroacetic acid (TFA, 570 mg, 5.00 mmol 10.0 equiv) under the flow of dry nitrogen. The reaction solution was stirred at room temperature for 1 h, which was then directly subjected to flash chromatography on silica gel using a mixture hexane/ethyl acetate 2:1 (v/v) as eluent to afford the β-keto ester product methyl (1*S*,2*R*,3*R*)-2-benzoyl-3-methyl-4-oxocyclobutane-1-carboxylate (**4b**) as a colorless oil (110.8 mg, 90% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.07 (d, 2H, J = 7.5 Hz), 7.64 (t, 1H, J = 7.5 Hz), 7.53 (t, 2H, J = 7.5 Hz), 4.66 (dd, 1H, J = 8.0, 2.5 Hz), 4.19 (dd, 1H, J = 8.0, 8.0 Hz), 3.78 (s, 3H), 3.70 (ddt, 1H, J = 8.0, 7.0, 2.5 Hz), 1.35 (d, 3H, J = 7.0 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 199.0, 197.4, 166.4, 135.5, 134.3, 129.1, 129.1, 129.0, 64.2, 58.3, 53.0, 41.1, 13.0 ppm. HRMS (ESI): m/z calcd for $C_{13}H_{13}O_4$ [M + H]$^+$ 247.0965, found 247.0967.

General Procedure for Retro-Claisen Ring-Opening Reaction of β-Keto Ester 4b with Nucleophile 2 (Scheme 4). To an oven-dried 8 mL screw-capped vial equipped with a magnetic stirring bar were added sequentially β-ketoester **4b** (24.6 mg, 0.100 mmol, 1.00 equiv), dry DCM (1.00 mL, 0.100 M), 4-dimethylaminopyridine (DMAP, 2.40 mg, 0.0200 mmol, 0.200 equiv), and nucleophile **2** (1.10 equiv) under the flow of dry nitrogen. The reaction solution was then stirred at room temperature under an atmosphere of dry nitrogen for the specified time as the reaction progress was monitored by TLC. After the completion, the reaction solution was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel to afford product **5b**.

*(2R,3S)-3-Benzoyl-5-methoxy-2-methyl-5-oxopentanoic Acid (**5bo**).* DCM/MeOH 95:5 (v/v) as eluent. 19.7 mg, 80% yield. Colorless oil. 99% ee [HPLC conditions: Chiralpak AD-H column, hexanes/*i*PrOH = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 17.5 min for major isomer, t_R = 20.7 min for minor isomer]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.02 (d, 2H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.49 (t, 2H, J = 7.5 Hz), 4.18 (br, 1H), 3.58 (s, 3H), 3.00 (dd, 1H, J = 16.5, 10.0 Hz), 2.91−2.79 (m, 1H), 2.65 (dd, 1H, J = 16.5, 3.5 Hz), 1.15 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 201.9, 179.5, 172.5, 137.5, 133.5, 128.9, 128.7, 52.1, 44.2, 42.0, 35.0, 15.8 ppm. HRMS (ESI): m/z calcd for $C_{14}H_{17}O_5$ [M + H]$^+$ 265.1071, found 265.1070.

*Dimethyl (2R,3S)-3-Benzoyl-2-methylpentanedioate (**5bp**).* Hexane/ethyl acetate 3:1 (v/v) as eluent. 25.9 mg, 93% yield. Colorless oil. 98% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 12.7 min for major isomer, t_R = 15.0 min for minor isomer]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.00 (d, 2H, J = 7.5 Hz), 7.56 (t, 1H, J = 7.5 Hz), 7.48 (t, 2H, J = 7.5 Hz), 4.22−4.15 (m, 1H), 3.62 (s, 3H), 3.58 (s, 3H), 2.97 (dd, 1H, J = 16.5, 10.0 Hz), 2.83 (dq, 1H, J = 10.0, 6.9 Hz), 2.55 (dd, 1H, J = 16.5, 3.5 Hz), 1.10 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 201.8, 174.8, 172.5, 137.7, 133.4, 128.8, 128.6, 52.0, 52.0, 44.3, 42.1, 35.0, 15.6 ppm. HRMS (ESI): m/z calcd for $C_{15}H_{19}O_5$ [M + H]$^+$ 279.1227, found 279.1224.

*Methyl (3S,4R)-3-Benzoyl-5-(benzylthio)-4-methyl-5-oxopentanoate (**5bq**).* Hexane/ethyl acetate 4:1 (v/v) as eluent. 35.6 mg, 96% yield. Colorless oil. 98% ee [HPLC conditions: Chiralpak OD-H column, hexanes/*i*PrOH = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 10.5 min for major isomer, t_R = 12.3 min for minor isomer]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (d, 2H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.48 (t, 2H, J = 7.5 Hz), 7.35−7.19 (comp, 5H), 4.31−4.23 (m, 1H), 4.18−4.04 (comp, 2H), 3.55 (s, 3H), 3.06−2.87 (comp, 2H), 2.58 (dd, 1H, J = 16.5, 3.5 Hz), 1.09 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 202.0, 201.0, 172.2, 137.9, 137.1, 133.5, 128.9, 128.8, 128.8, 128.7, 127.5, 51.9, 50.6, 44.0, 35.6, 33.5, 16.8 ppm. HRMS (ESI): m/z calcd for $C_{21}H_{23}O_4S$ [M + H]$^+$ 371.1312, found 371.1302.

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*Methyl (3S,4R)-3-Benzoyl-4-methyl-5-oxo-5-(phenylamino)-pentanoate (**5br**).* Hexane/ethyl acetate 2:1 (v/v) as eluent. 28.2 mg, 83% yield. Colorless oil. [HPLC conditions: Chiralpak IA column, hexanes/*i*PrOH = 80:20, flow rate = 1.0 mL/min, wavelength = 254 nm, t_R = 9.0 min for minor isomer, t_R = 10.7 min for major isomer]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.07 (d, 2H, J = 7.5 Hz), 7.98 (br, 1H), 7.61 (t, 1H, J = 7.5 Hz), 7.58−7.45 (comp, 4H), 7.33 (t, 2H, J = 7.5 Hz), 7.12 (t, 1H, J = 7.5 Hz), 4.33−4.21 (m, 1H), 3.55 (s, 3H), 2.94 (dd, 1H, J = 16.5, 10.0 Hz), 2.88−2.78 (m, 1H), 2.70 (dd, 1H, J = 16.5, 3.5 Hz), 1.16 (d, 3H, J = 6.9 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ 203.0, 172.3, 172.2, 137.7, 137.5, 133.6, 129.0, 128.9, 128.7, 124.5, 119.9, 51.9, 44.7, 44.3, 35.6, 16.7 ppm. HRMS (ESI): m/z calcd for $C_{20}H_{22}NO_4$ $[M + H]^+$ 340.1543, found 340.1557.

Procedure for Lithium Aluminum Hydride Reduction of 3ab. To an oven-dried 8 mL screw-capped vial equipped with a magnetic stirring bar were added **3ab** (30.3 mg, 0.100 mmol, 1.00 equiv) and dry Et_2O (1.00 mL, 0.100 M). The resulting solution was cooled to 0 °C, and $LiAlH_4$ (LAH, 38.0 mg, 1.00 mmol, 10.0 equiv) was added in portions. The suspension was stirred for 10 min, and water (ca. 2 mL) was then added to quench the reaction. The mixture was stirred for another 30 min, filtered and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a 10:1 (v/v) mixture of DCM/MeOH as eluent to afford 5-hydroxy-3-(hydroxy(phenyl)methyl)-1-(pyrrolidin-1-yl)-pentan-1-one (**6**) as a colorless oil (24.0 mg, 86% yield, dr = 2.6:1). ^{1}H NMR [for mixture of diastereomers] ($CDCl_3$, 500 MHz): δ 7.37−7.29 (comp, 13H), 7.27−7.21 (comp, 5H), 4.77 (d, 2.6H, J = 5.0 Hz), 4.73 (d, 1H, J = 5.0 Hz), 4.45 (br, 1H), 3.94 (br, 2.6H), 3.73−3.51 (comp, 7.2 H), 3.50−3.37 (comp, 7.2H), 3.34−3.27 (comp, 7.2H), 2.65−2.41 (m, 7.2H), 2.28−2.18 (comp, 3.6H), 2.00−1.70 (comp, 18H), 1.66−1.56 (m, 1H), 1.53−1.43 (m, 2.6H) ppm. ^{13}C{^{1}H} NMR [for mixture of diastereomers] ($CDCl_3$, 126 MHz): δ 172.1, 171.7, 144.0, 143.1, 128.4, 128.3, 127.4, 127.2, 126.6, 126.3, 76.9, 76.5, 60.5, 47.0, 46.9, 46.1, 39.1, 38.9, 36.4, 34.9, 34.3, 33.1, 26.2, 24.5 ppm. HRMS (ESI): m/z calcd for $C_{16}H_{24}NO_3$ $[M + H]^+$ 278.1751, found 278.1752.

Procedure for the Hofmann Rearrangement of 3ae. Compound **7** was synthesized according to the reported procedure.[21b] To an oven-dried 8 mL screw-capped vial equipped with a magnetic stirring bar were sequentially added **3ae** (24.9 mg, 0.100 mmol, 1.00 equiv), MeCN (1.00 mL, 0.100 M), *I,I*-bis(trifluoroacetoxy)-iodobenzene (PIFA, 60.2 mg, 0.140 mmol, 1.40 equiv), and water (3.60 mg, 0.200 mmol, 2.00 equiv). After being stirred for 12 h, the mixture was heated at 60 °C in an oil bath for 30 min to decompose the remaining PIFA and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a 10:1 mixture of DCM/MeOH (v/v) as eluent to afford 2-benzoyl-4-methoxy-4-oxobutan-1-aminium trifluoroacetate (**7**) as a pale yellow oil (30.2 mg, 90% yield). ^{1}H NMR (CD_3OD, 300 MHz): δ 8.02 (d, 1H, J = 7.5 Hz), 7.67 (t, 1H, J = 7.5 Hz), 7.55 (t, 1H, J = 7.5 Hz), 4.32−4.19 (m, 1H), 3.63 (s, 1H), 3.43 (dd, 1H, J = 13.2, 7.2 Hz), 3.15 (dd, 1H, J = 13.2, 5.4 Hz), 2.90 (dd, 1H, J = 17.1, 5.4 Hz), 2.71 (dd, 1H, J = 17.1, 7.2 Hz) ppm. ^{13}C{^{1}H} NMR (CD_3OD, 126 MHz): δ 200.8, 172.8, 163.1 (q, J = 35.8 Hz), 136.6, 135.1, 130.1, 129.7, 118.1 (q, J = 293.0 Hz), 52.6, 42.0, 40.8, 35.2 ppm. HRMS (ESI): m/z calcd for $C_{12}H_{16}NO_3^+$ $[M]^+$ 222.1125, found 222.1125.

Procedure for the Synthesis of Furan 8. Compound **8** was synthesized according to the reported procedure.[22] To an oven-dried 8 mL screw-capped vial equipped with a magnetic stirring bar were added **3aa** (33.9 mg, 0.100 mmol, 1.00 equiv), dry DCM (1.00 mL, 0.100 M), and pyridine (79.1 mg, 1.00 mmol, 10.0 equiv). The solution was cooled to −78 °C, and trifluoroacetic anhydride (TFAA, 44.1 mg, 0.210 mmol, 2.10 equiv) was added dropwise. After being stirred for 30 min at −78 °C, the mixture was warmed to room temperature and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel using a 2:1 (v/v) mixture of hexane/ethyl acetate as eluent to afford methyl 2-[5-(*N*-benzyl-2,2,2-trifluoroacetamido)-2-phenylfuran-3-yl]acetate (**8**) as a colorless oil (39.2 mg, 94% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.52 (d, 2H, J = 7.5 Hz), 7.44 (t, 2H, J = 7.5 Hz), 7.39−7.26 (comp, 6H), 6.16 (s, 1H), 4.91 (s, 2H), 3.71 (s, 3H), 3.59 (s, 2H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 171.1, 157.6 (q, J = 36.2 Hz), 149.1, 142.4, 134.9, 129.8, 129.1, 128.9, 128.8, 128.5, 128.4, 126.6, 116.2 (q, J = 288.4 Hz), 114.4, 111.3, 54.0, 52.3, 31.8 ppm. HRMS (ESI): m/z calcd for $C_{22}H_{18}F_3NO_4$ $[M + H]^+$ 418.1261, found 418.1257.

Procedure for the Synthesis of Thiophene 9. Compound **9** was synthesized according to the reported procedure.[23] To an oven-dried 8 mL screw-capped vial equipped with a magnetic stirring bar were sequentially added **3ab** (30.3 mg, 0.100 mmol, 1.00 equiv), toluene (1.00 mL, 0.100 M), and Lawesson's reagent (48.5 mg, 0.120 mmol, 1.20 equiv). After being stirred under reflux in an oil bath for 4 h, the mixture was cooled to room temperature and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel using a 3:1 (v/v) mixture of hexane/ethyl acetate as eluent to afford methyl 2-(2-phenyl-5-(pyrrolidin-1-yl)thiophen-3-yl)acetate (**9**) as a pale yellow oil (25.0 mg, 83% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44 (d, 2H, J = 7.5 Hz), 7.37 (t, 2H, J = 7.5 Hz), 7.25 (t, 1H, J = 7.5 Hz), 5.73 (s, 1H), 3.73 (s, 3H), 3.60 (s, 2H), 3.31−3.26 (comp, 4H), 2.07−1.97 (comp, 4H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 172.3, 154.1, 134.7, 129.0, 128.7, 128.7, 126.4, 123.2, 102.6, 52.2, 50.7, 35.1, 25.9. ppm. HRMS (ESI): m/z calcd for $C_{17}H_{20}NO_2S$ $[M + H]^+$ 302.1209, found 302.1216.

Procedure for the Synthesis of 1,5-Dihydro-2*H*-pyrrol-2-one 10. Compound **10** was synthesized according to the reported procedure.[24] To an oven-dried 8 mL screw-capped vial equipped with a magnetic stirring bar were sequentially added **3aa** (33.9 mg, 0.100 mmol, 1.00 equiv), dry MeCN (1.00 mL, 0.100 M), and $Al(OTf)_3$ (23.7 mg, 0.050 mmol, 0.500 equiv). After being stirred under reflux in an oil bath for 4 h, the mixture was cooled to room temperature, diluted with water (ca. 3 mL), and then extracted with ethyl acetate (3 × 3 mL). The combined organic layer was washed with brine (ca. 3 mL) and dried over anhydrous $MgSO_4$ (ca. 1 g). After filtration and concentration under reduced pressure, the residue was purified by flash chromatography on silica gel using a 3:1 (v/v) mixture of hexane/ethyl acetate as eluent to afford methyl 2-(1-benzyl-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl)acetate (**10**) as a colorless oil (27.3 mg, 85% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39−7.34 (comp, 3H), 7.30−7.23 (comp, 3H), 7.11−7.09 (comp, 2H), 7.06−7.02 (comp, 2H), 6.20 (s, 1H), 5.15 (d, 1H, J = 15.0 Hz), 4.92 (s, 1H), 3.61 (s, 3H), 3.59 (d, 1H, J = 15.0 Hz), 3.19 (d, 1H, J = 17.0 Hz), 2.96 (d, 1H, J = 17.0 Hz) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ 170.9, 169.4, 154.8, 137.4, 134.3, 129.4, 129.2, 128.8, 128.4, 128.4, 127.6, 124.5, 67.6, 52.4, 43.9, 34.0 ppm. HRMS (ESI): m/z calcd for $C_{20}H_{20}NO_3$ $[M + H]^+$ 322.1438, found 322.1442.

Procedure for the Large-Scale Synthesis of Methyl 3-Benzoyl-5-oxo-5-(pyrrolidin-1-yl)pentanoate (3ab). To an oven-dried 50 mL round-bottomed flask equipped with a magnetic stirring bar were added donor−acceptor cyclobutene **1a** (388.6 mg, 1.00 mmol, 1.00 equiv) and wet nitromethane (0.1% of water) (20.0 mL, 0.0500 M). Pyrrolidine **2b** (74.7 mg, 1.05 mmol, 1.05 equiv) was then added in one portion to the stirred reaction solution, and stirring was continued at room temperature for 20 min as the reaction progress was monitored by TLC. After disappearance of **1a**, the reaction solution was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel using a 1:4 (v/v) mixture of hexane/ethyl acetate as eluent to afford product **3ab** (296.4 mg, 0.980 mmol, 98%) as a colorless oil.

Procedure for the Large-Scale Synthesis of Methyl 5-[(2-[1*H*-Indol-3-yl]ethyl)amino]-3-benzoyl-5-oxopentanoate (3ag). To an oven-dried 50 mL round-bottomed flask equipped with a magnetic stirring bar were added donor−acceptor cyclobutene **1a** (500.0 mg, 1.29 mmol, 1.00 equiv) and wet nitromethane (0.1% of water) (25.8 mL, 0.0500 M). Tyrptamine **2g** (216.5 mg, 1.35 mmol, 1.05 equiv) was then added in one portion to the stirring reaction solution, and stirring was continued at room temperature for 2 h as the reaction progress was monitored by TLC. After disappearance of **1a**, the reaction solution was concentrated under reduced pressure,

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and the residue was purified by flash chromatography on silica gel using a 1:2 (v/v) mixture of hexane/ethyl acetate as eluent to afford product **3ag** (474.7 mg, 1.21 mmol, 94%) as a colorless oil.

Procedure for the Large-Scale Synthesis of Methyl *trans*-2-Benzoyl-4-oxocyclobutane-1-carboxylate (4a). To an oven-dried 8 mL screw-capped vial equipped with a magnetic stirring bar were sequentially added cyclobutene **1a** (1.0 g, 2.57 mmol, 1.00 equiv), dry $CHCl_3$ (1.3 mL, 2.00 M), and trifluoroacetic acid (TFA, 2.93 g, 25.74 mmol 10.0 equiv) under the flow of dry nitrogen. The reaction solution was stirred at room temperature for 1 h, as the reaction progress was monitored by TLC. After disappearance of **1a**, the reaction solution was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel using a 2:1 (v/v) of hexane/ethyl acetate as eluent to afford product **4a** (567.8 mg, 2.44 mmol, 95% yield) as a colorless oil.

Procedure for the Large-Scale Synthesis of Dimethyl 3-benzoylpentanedioate (3ap). To an oven-dried 50 mL round-bottomed flask equipped with a magnetic stirring bar were added sequentially β-keto ester **4a** (567.8 mg, 2.44 mmol, 1.00 equiv), dry DCM (24.4 mL, 0.100 M), 4-dimethylaminopyridine (DMAP, 59.7 mg, 0.490 mmol, 0.200 equiv), and methanol (86.2 mg, 2.69 mmol, 1.10 equiv) under the flow of dry nitrogen. The reaction solution was then stirred at room temperature under an atmosphere of dry nitrogen for 24 h, as the reaction progress was monitored by TLC. After completion, the reaction solution was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel using a 3:1 (v/v) of hexane/ethyl acetate as eluent to afford product **3ap** (581.5 mg, 2.20 mmol, 90% yield) as a colorless oil.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01176.

Experimental details concerning reaction rates (Scheme 2) and deuterium incorporation (Scheme 8); copies of ^1H and $^{13}C\{^1H\}$ NMR spectra of new compounds; ^2H NMR spectra for deuterated products; HPLC traces for racemic and chiral compounds (PDF)

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Notes

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