Formation of Complex α-Imino Esters via Multihetero-Cope Rearrangement of α-Keto Ester Derived Nitrones

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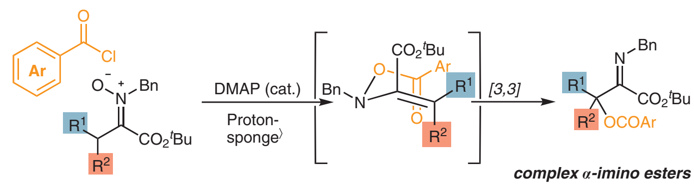

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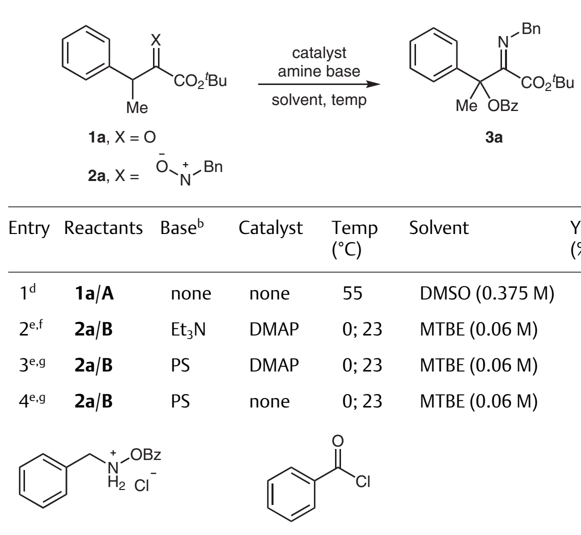
Abstract A sequential benzoylation and multihetero-Cope rearrangement of α-keto ester derived nitrones has been developed. The reaction furnishes a diverse array of complex α-imino ester derivatives. The products can be transformed into amino alcohols via $LiAlH_4$ reduction.

Key words rearrangement, ketones, imines, oxygenations, esters

Fragmentation of weak N–O σ-bonds (bond strength ~57 kcal/mol) can be leveraged during the synthesis of complex organic frameworks, and a comprehensive review of the rearrangement of *N*-oxyenamine derivatives has been penned by Tabolin and Ioffe.[3] Within this subclass of N–O bond-cleaving reactions, sigmatropic rearrangements of *O*-acyl- and *O*-imidoyl-*N*-oxyenamines can provide α-hydroxy or α-amino carbonyl derivatives, which are valuable intermediates and key structural elements of natural and unnatural bioactive compounds. An early report by Coates and Cummins provided a method for the rearrangement of *N*-vinyl-*O*-acylhydroxylamines resulting from acylation of nitrones with acid chlorides (Scheme 1, a).[4] More recently, Tomkinson and co-workers disclosed the design of *N*-alkyl-*O*-acylhydroxylamine reagents that facilitate the synthesis of α-hydroxy carbonyl derivatives by way of a tandem condensation/rearrangement process (Scheme 1, b).[5] Alternatively, the use of a Cbz-protected trifluoromethyl imidoyl chloride led to α-amination of nitrones analogous to the α-oxygenation developed by Coates (Scheme 1, c).[6] The development of methods for the synthesis of β-branched α-keto esters is a topic of ongoing interest,[7–9] and the functionalization of such compounds via *N*-oxyenamine rearrangements appealed to us as a means to generate complex α-imino esters containing fully substituted β-stereocenters (Scheme 1, d). Following rearrangement, the C=N π-bond could, in principle, react with nucleophiles, providing access to novel amino acid derivatives possessing contiguous stereocenters.

We initially chose to focus on the β-benzoylation of α-keto ester derived *O*-benzoyl-*N*-oxyenamines. We first tested condensation of α-keto ester **1a** with the Tomkinson reagent **A** (Table 1, entry 1). Presumably this reaction was

Table 1 Optimization of the Reaction Conditions[a]



Entry	Reactants	Base[b]	Catalyst	Temp (°C)	Solvent	Yield (%)[c]
1[d]	**1a**/**A**	none	none	55	DMSO (0.375 M)	0
2[e,f]	**2a**/**B**	Et_3N	DMAP	0; 23	MTBE (0.06 M)	48
3[e,g]	**2a**/**B**	PS	DMAP	0; 23	MTBE (0.06 M)	86
4[e,g]	**2a**/**B**	PS	none	0; 23	MTBE (0.06 M)	63

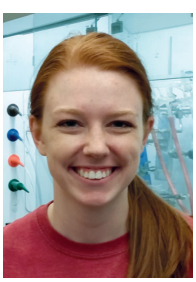
[a] All reactions run using 0.15 mmol of **1a** or **2a**.
[b] PS = Proton-sponge®.
[c] Yield of product isolated via column chromatography.
[d] 1.0 equiv **A** used.
[e] 4 Å molecular sieves (205 mg) were added to the reaction mixture; 0.2 equiv DMAP employed.
[f] 5.0 equiv Et_3N employed with 3.0 equiv **B**.
[g] 2.5 equiv Proton-sponge® employed with 2.0 equiv of **B**.

prevented by the sterically hindered ketone of **1a** coupled with low nucleophilicity of the free base of **A**. Heating a mixture of *N*-benzylhydroxylamine and α-keto ester **1a** furnished nitrone **2a**, which upon treatment with benzoyl chloride (**B**) in the presence of triethylamine and the nucleophilic catalyst 4-(dimethylamino)pyridine (DMAP) delivered the desired β-benzoylated imino ester **3a** in 48% yield (Table 1, entry 2). In this experiment, the corresponding α-keto ester resulting from hydrolysis of **3a** by adventitious water was observed in the ^{1}H NMR spectrum of the unpurified materials. Sequestration of acid is apparently crucial to the stability of **3a** under the reaction conditions as replacing triethylamine with the thermodynamically stronger base Proton-sponge® suppresses hydrolysis, allowing isolation of **3a** in 86% yield (Table 1, entry 3). Despite the sensitivity of **3a** under the conditions, it is completely stable toward chromatography on untreated silica gel. The reaction proceeds in the absence of DMAP, however the yield of **3a** is lower (Table 1, entry 4).

With suitable reaction conditions in hand, we began to explore the scope of α-imino esters that could be prepared (Scheme 2). The *p*-halogen series imines **3b–d** were obtained in high yield. In addition, an *o*-fluoro-substituted nitrone underwent the reaction in good yield to afford imino benzoate **3e**. Electron-rich nitrones were also viable substrates, and representative examples include imines **3f–3h**.

Biographical Sketches

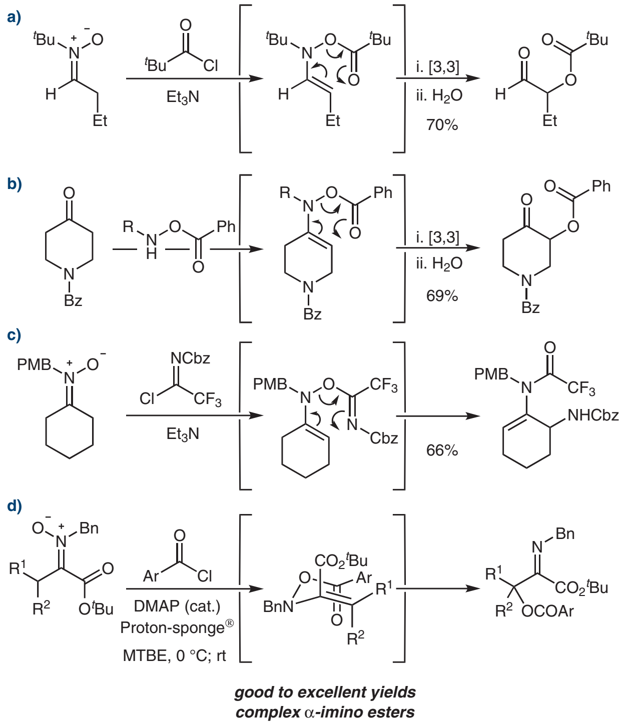
Samuel L. Bartlett received his B.S. in chemistry from Oregon State University in 2012 where he conducted research with Prof. Chris Beaudry. He completed his Ph.D. in the laboratory of Prof. Jeffrey S. Johnson at the University of North Carolina at Chapel Hill where he explored new catalytic enantioconvergent reactions. During his doctoral studies, he was also an NSF EAPSI Fellow with Prof. Mikiko Sodeoka and Dr. Yoshihiro Sohtome at RIKEN in Japan. There he worked on the development of new asymmetric reactions employing catalytically generated transition-metal enolates. He is currently a Medicinal Chemist at Enanta Pharmaceuticals.



Kimberly M. Keiter received her M.S. in analytics from North Carolina State University and her B.S. in applied mathematics and chemistry from the University of North Carolina at Chapel Hill. During her undergraduate years, she was a research assistant in the Johnson Group where she received the Matthew Neely Jackson Undergraduate Research Award. She is currently a Data Scientist at Elder Research where she analyzes clients' data to find actionable insights.

Blane P. Zavesky received his B.S. in chemistry from the University of Michigan in 2014 with high distinction and honors in chemistry, where he conducted research under Prof. John P. Wolfe. He began his Ph.D. studies at the University of North Carolina in 2014, working in the laboratories of Prof. Jeffrey S. Johnson. His research focuses on the total synthesis of biologically active alkaloid natural products.

Jeffrey S. Johnson received his B.S. in chemistry from the University of Kansas in 1994 with highest distinction and honors in chemistry. He was a graduate student at Harvard University as an NSF Graduate Fellow in the laboratories of Prof. David A. Evans, receiving his Ph.D. in 1999. He conducted postdoctoral research at the University of California at Berkeley from 1999 to 2001 as an NIH Postdoctoral Fellow under the direction of Prof. Robert G. Bergman. He joined the faculty of the Department of Chemistry at the University of North Carolina at Chapel Hill in 2001, where he is currently the A. Ronald Gallant Distinguished Professor and the department chairperson.



Scheme 1 Functionalization of carbonyl derivatives via *O*-acyl- and *O*-imidoyl-*N*-oxyenamine rearrangement

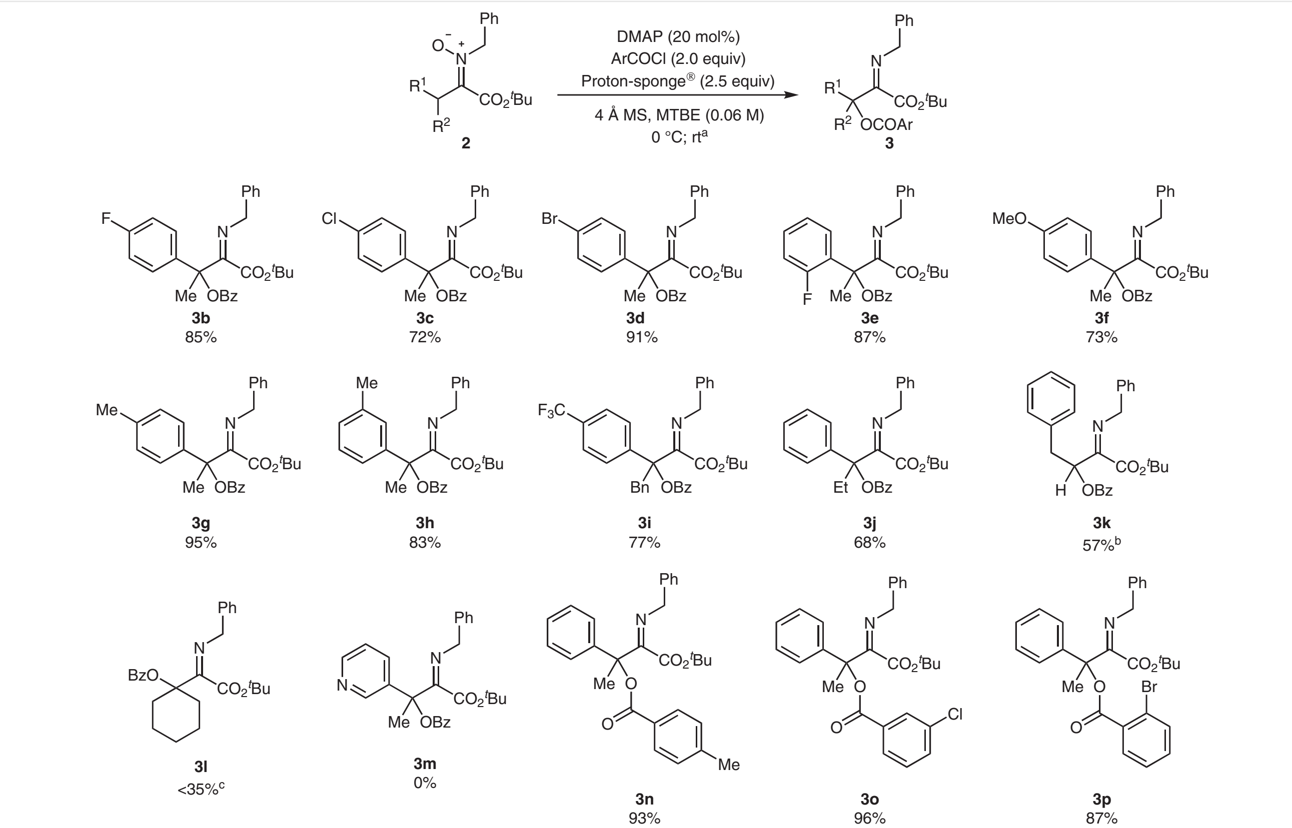
Larger alkyl substituents were tolerated at the β-position, and β-benzyl-substituted tertiary benzoate **3i** as well as the ethyl derivative **3j** could be obtained in good and moderate yield, respectively. The secondary benzoate **3k** could be formed under the reaction conditions; however, this product decomposed on silica gel and an NMR yield is provided in Scheme 2.[10] All other products were stable toward chromatography on untreated silica gel. The cyclohexyl derivative **3l** was furnished in less than 35% yield (NMR yield) and could not be separated from impurities, while the desired pyridyl-substituted derivative **3m** was not formed under the reaction conditions. Other aroyl chlorides could also be used in the reaction, and *p*-methylbenzoate **3n**, *m*-chlorobenzoate **3o**, as well as *o*-bromobenzoate **3p** were obtained in high yield.

Preliminary attempts to selectively functionalize the azomethine functionality in the rearrangement products have been unsuccessful, most likely due to the sterically encumbered nature of these electrophiles. At this stage, the utility of the products has been demonstrated by exhaustive $LiAlH_4$ reduction of **3a** and **3f**, which delivered the corresponding amino alcohols **4a** and **4f** in intermediate yield and diastereoselectivity (Scheme 3). The relative stereochemistry of the major diastereomer was established via synthesis of the cyclic carbamate **5f**, which exhibited the illustrated NOESY interactions between the methyl protons and the methine proton.

In summary, we have developed a sequential benzoylation–multihetero-Cope rearrangement of α-keto ester derived nitrones. The reaction furnishes complex α-imino ester derivatives in good to excellent yield. The products can be transformed into complex amino alcohols via $LiAlH_4$ reduction. Further exploration of the reactivity of these products, with a particular focus on accessing complex amino acid derivatives via selective functionalization of the imine moiety, is currently underway in our laboratory.

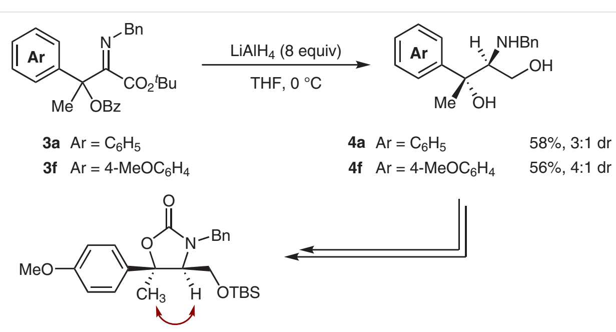
Unless noted otherwise, all experiments were carried out in a flame-dried round-bottomed flask under a stream of nitrogen gas. ^1H and ^{13}C NMR spectra were obtained on a Bruker DRX 600 (^1H, 600 MHz; ^{13}C, 150 MHz), Bruker 500 (^1H, 500 MHz; ^{13}C, 125 MHz), or Bruker DRX 400 (^1H, 400 MHz; ^{13}C, 100 MHz) spectrometer. ^1H NMR data are reported as follows: chemical shift, multiplicity (standard abbreviations), coupling constant(s) (Hz), and relative integration. For HRMS, all samples were prepared in MeOH. The HPLC system consisted of an Agilent 1200 binary pump (G1312A) operating at a flow rate of 0.3 $mL \cdot min^{-1}$. The solvents were degassed using an on-line membrane system (Agilent G1379A). The column was maintained in a thermostated compartment at 40 °C (Agilent G1316A). The diode array detector (Agilent G1315D) was operated at three wavelengths (250, 254, and 280 nm). Separation was performed on a Waters Acquity UPLC BEH C18 column (2.1 × 50 mm, 1.7 μm particle size). The injection (5 μL) was performed using an autosampler (Agilent G1329A). LC conditions were set at water with 0.1% formic acid (A) for 1 min, before ramping linearly over 5 min to 100% acetonitrile with 0.1% formic acid (B), and then switched back to 100% A and allowed to re-equilibrate until 10 min. The HPLC system was coupled to the Q-TOF system via a dual ESI interface operating in positive ion mode using a capillary voltage of +3.5 kV. The other optimum values of the ESI-TOF parameters were drying gas temperature 325 °C, drying gas flow 5 $L \cdot min^{-1}$, and nebulizing gas pressure 15 psi. Detection was carried out considering a mass range of 100–1500 *m*/*z*. Prior to acquiring samples, an external instrument calibration was performed using Agilent ESI-L Low Concentration Tuning Mix. MassHunter Quantitative Analysis (Agilent) was used to analyze the data. Solutions were dissolved in MeOH at 0.1 $mg \cdot mL^{-1}$ or less, and diluted appropriately based on responsiveness to the ESI mechanism. Molecular formula assignments were determined with Molecular Formula Calculator (v 1.2.3). The success of mass data for molecular ions was considered based on the widely accepted accuracy threshold for confirmation of elemental compositions established at 5 ppm. All observed species were singly charged, as verified by unit *m*/*z* separation between mass spectral peaks corresponding to the ^{12}C and $^{13}C^{12}C_{c-1}$ isotope for each elemental composition. IR spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. TLC was performed on Sorbtech plastic-backed 0.20 mm silica gel 60 plates. Visualization was accomplished with UV light and either an aqueous ceric ammonium molybdate (CAM) or $KMnO_4$ solution, followed by heating. Flash chromatography was performed under positive nitrogen pressure using SiliaFlash-P60 silica gel (40–63 μm) purchased from SiliCycle.

Et_3N was purified and dried by passing through a column of activated alumina. DMAP and ^{t}BuOH were purchased from Sigma-Aldrich and used without further purification. Benzoyl chloride was purchased from Acros and used without further purification. Methyl *tert*-butyl ether (MTBE) was purified via distillation from calcium hydride and stored over activated 13X-type molecular sieves (bead form). The pro-



Scheme 2 Scope of the rearrangement reaction. [a] All reactions were conducted on 0.15 mmol scale. The reactions were monitored by silica gel TLC and were generally complete within 4 h. [b] Product is unstable to silica gel; yield was obtained via ^1H NMR analysis using mesitylene as an internal standard. [c] Product could not be separated from impurities; yield was obtained via ^1H NMR analysis using mesitylene as an internal standard.

cedures for the preparation of *tert*-butyl 2-oxo-4-phenylbutanoate (**1k**)[11] and *tert*-butyl 2-oxo-4-phenyl-3-(4-(trifluoromethyl)phenyl)-butanoate (**1i**)[12] are reported in the literature.



Scheme 3 $LiAlH_4$ reduction of products **3a** and **3f** and determination of diastereoselectivity via NOESY experiments with the derived cyclic carbamate **5f**

tert-Butyl α-Keto Esters 1; General Procedure

Step 1: The ethyl 2-oxo-3-arylbutanoate (4.46 mmol), prepared in two steps via a literature method,[11] was added neat to a 25-mL round-bottomed flask equipped with a stir bar. Next, aqueous NaOH (3 M, 4 mL) was added and the reaction mixture was stirred for 24 h at rt. The mixture was then acidified (pH ~5) with aqueous HCl (3 M), and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over $MgSO_4$. Filtration through a plug of cotton and concentration delivered the corresponding α-keto acid which was carried on without purification. Step 2: The crude α-keto acid from step 1 was dissolved in CH_2Cl_2 (4.5 mL), and several small drops of DMF were added. The reaction mixture was cooled to 0 °C using an ice–water bath, and oxalyl chloride (0.57 mL, 6.69 mmol, 1.5 equiv) was slowly added. The reaction mixture was stirred for 20 h and concentrated. Residual oxalyl chloride was removed under reduced pressure. The acid chloride was immediately used in the next step without purification. Step 3: ^{t}BuOH (1.27 mL, 13.4 mmol, 3.0 equiv) and pyridine (719 μL, 8.92 mmol, 2.0 equiv) were dissolved in CH_2Cl_2 (4.5 mL, 1 M), and the mixture was cooled to 0 °C using an ice–water bath. The acid chloride from step 2 was slowly added in CH_2Cl_2 (1.96 mL, 2.3 M). The reaction mixture was stirred for 24 h, then diluted with water. The aqueous phase was extracted three times with CH_2Cl_2 (20 mL), and the combined organic layers were dried over $MgSO_4$. The product was purified by silica gel column chromatography.

tert-Butyl 2-Oxo-3-phenylbutanoate (1a)

Prepared from ethyl 2-oxo-3-phenylbutanoate. Purified by silica gel column chromatography using 5% EtOAc/hexanes (636 mg, 61% yield).

IR (thin film): 3446, 3030, 2980, 2035, 2875, 2319, 1744, 1725, 1494, 1455, 1371, 1259, 1164, 1120, 1023, 839 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.31–7.35 (m, 2 H), 7.24–7.28 (m, 1 H), 7.19–7.21 (m, 2 H), 4.34 (q, *J* = 6.92 Hz, 1 H), 1.44 (d, *J* = 7.0 Hz, 3 H), 1.33 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.2, 161.0, 138.1, 128.9, 122.5, 127.5, 83.9, 48.8, 27.6, 16.6.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{18}O_3$[M + Na]: 257.1154; found: 257.1148.

tert-Butyl 3-(4-Fluorophenyl)-2-oxobutanoate (1b)

Prepared from ethyl 3-(4-fluorophenyl)-2-oxobutanoate. Purified by silica gel column chromatography using 2.5% EtOAc/hexanes (819 mg, 46% yield).

IR (thin film): 2981, 2937, 1732, 1603, 1509, 1457, 1395, 1371, 1259, 1225, 1161, 1135, 1026, 841, 759 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14–7.18 (m, 2 H), 6.97–7.03 (m, 2 H), 4.34 (q, *J* = 7.0 Hz, 1 H), 1.41 (d, *J* = 7.0 Hz, 3 H), 1.34 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 194.7, 162.1 (d, $J_{19F-13C}$ = 244.7 Hz), 160.8, 133.8 (d, $J_{19F-13C}$ = 3.0 Hz), 130.1 (d, $J_{19F-13C}$ = 8.2 Hz), 115.7 (d, $J_{19F-13C}$ = 21.7 Hz), 84.0, 47.7, 27.5, 16.5.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{17}FO_3$ [M + Na] : 275.1059; found: 275.1057.

tert-Butyl 3-(4-Chlorophenyl)-2-oxobutanoate (1c)

Prepared from ethyl 3-(4-chlorophenyl)-2-oxobutanoate. Purified by silica gel column chromatography using 2.5% EtOAc/hexanes (519 mg, 47% yield).

IR (thin film): 3446, 2981, 2936, 2875, 2294, 1724, 1594, 1493, 1457, 1410, 1395, 1371, 1259, 1163, 1093, 1026, 836 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.5 Hz, 2 H), 7.15 (d, *J* = 8.5 Hz, 2 H), 4.35 (q, *J* = 7.0 Hz, 1 H), 1.42 (d, *J* = 7.0 Hz, 3 H), 1.38 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 194.6, 160.7, 136.6, 133.5, 129.8, 129.0, 84.2, 47.9, 27.6, 16.7.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{17}ClO_3$ [M + Na]: 291.0764; found: 291.0756.

tert-Butyl 3-(4-Bromophenyl)-2-oxobutanoate (1d)

Prepared from ethyl 3-(4-bromophenyl)-2-oxobutanoate using Procedure A. Purified by silica gel column chromatography using 2.5% ethyl acetate/hexanes (531 mg, 48% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (d, *J* = 8.4 Hz, 2 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 4.34 (q, *J* = 7.0 Hz, 1 H), 1.42 (d, *J* = 7.0 Hz, 3 H), 1.38 (s, 9 H)

tert-Butyl 3-(2-Fluorophenyl)-2-oxobutanoate (1e)

Prepared from ethyl 3-(2-fluorophenyl)-2-oxobutanoate. Purified by silica gel column chromatography using 2.5% EtOAc/hexanes (681 mg, 61% yield).

IR (thin film): 2981, 2937, 2877, 2357, 2321, 1746, 1732, 1507, 1492, 1456, 1395, 1371, 1258, 1163, 1123, 1023, 830, 758 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.28 (m, 1 H), 7.04–7.11 (m, 3 H), 4.57 (q, *J* = 7.0 Hz, 1 H), 1.43 (d, *J* = 7.0 Hz, 3 H), 1.33 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 194.6, 160.5, 160.4 (d, $J_{19F-13C}$ = 245 Hz), 129.3 (d, $J_{19F-13C}$ = 6.8 Hz), 129.3 (d, $J_{19F-13C}$ = 11.0 Hz), 125.9 (d, $J_{19F-13C}$ = 15.6 Hz), 124.5 (d, $J_{19F-13C}$ = 4.2 Hz), 115.7 (d, $J_{19F-13C}$ = 21.8 Hz), 84.1, 42.0 (d, $J_{19F-13C}$ = 2.5 Hz), 27.5, 15.7.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{17}FO_3$ [M + Na]: 275.1059; found: 275.1055.

tert-Butyl 3-(4-Methoxyphenyl)-2-oxobutanoate (1f)

Prepared from ethyl 3-(4-methoxyphenyl)-2-oxobutanoate. Purified by silica gel column chromatography using 2.5% EtOAc/hexanes (1.12 g, 59% yield).

IR (thin film): 2979, 2936, 2838, 1742, 1721, 1610, 1513, 1457, 1395, 1371, 1303, 1254, 1179, 1122, 1026, 837 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.7 Hz, 2 H), 4.30 (q, *J* = 7.0 Hz, 1 H), 3.78 (s, 3 H), 1.41 (d, *J* = 7.0 Hz, 3 H), 1.36 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.2, 161.2, 159.0, 129.8, 129.7, 114.3, 83.8, 55.3, 47.7, 27.6, 16.6.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{20}O_4$ [M + Na]: 287.1259; found: 287.1248.

tert-Butyl 2-Oxo-3-(*p*-tolyl)butanoate (1g)

Prepared from ethyl 2-oxo-3-(*p*-tolyl)butanoate. Purified by silica gel column chromatography using 2.5% EtOAc/hexane and subsequently CH_2Cl_2 (2.20 g, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08–7.14 (m, 4 H), 4.31 (q, *J* = 7.3 Hz, 1 H), 2.32 (s, 3 H), 1.42 (d, *J* = 7.3 Hz, 3 H), 1.35 (s, 9 H).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{20}O_3$ [M + Na]: 271.1310; found: 271.1304.

tert-Butyl 2-Oxo-3-(*m*-tolyl)butanoate (1h)

Prepared from ethyl 2-oxo-3-(*m*-tolyl)butanoate. Purified by silica gel column chromatography using 2.5% EtOAc/hexane (252 mg, 23% yield).

IR (thin film): 2979, 2934, 1770, 1744, 1724, 1607, 1457, 1370, 1282, 1258, 1166, 1119, 1025, 851, 784, 703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.23 (m, 1 H), 7.06–7.08 (m, 1 H), 6.99–7.01 (m, 2 H), 4.31 (q, *J* = 7.0 Hz, 1 H), 2.32 (s, 3 H), 1.43 (d, *J* = 7.0 Hz, 3 H), 1.34 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.1, 161.0, 138.4, 137.8, 129.1, 128.7, 128.1, 125.5, 83.7, 48.6, 27.5, 21.2, 16.5.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{20}O_3$ [M + Na]: 271.1310; found: 271.1303.

ethyl-Butyl 2-Oxo-3-phenylpentanoate (1j)

Prepared from ethyl 2-oxo-3-(*m*-tolyl)butanoate. Purified by silica gel column chromatography using 2.5% EtOAc/hexane (773 mg, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.33 (m, 2 H), 7.25–7.27 (m, 1 H), 7.18–7.19 (m, 2 H), 4.14 (dd, *J* = 6.6, 8.2 Hz, 1 H), 2.06–2.14 (m, 1 H), 1.71–1.79 (m, 1 H), 1.34 (s, 9 H), 0.87 (t, *J* = 7.4 Hz, 3 H).

tert-Butyl 2-Cyclohexyl-2-oxoacetate (1l)

Compound **1l** was prepared via the procedure employed for compound **1k** with slight modification. Magnesium turnings (0.31 g, 12.7 mmol) were added to a flame-dried 25 mL round-bottomed flask equipped with a reflux condenser and a stir bar. The flask containing the magnesium turnings was held under direct flame using a Bunsen burner for 1 min while being flushed with nitrogen gas. Once the flask had returned to room temperature, THF (12.7 mL) was added. Bromocyclohexane (2.00 g, 12.7 mmol, 1.53 mL) was slowly added via syringe. The mixture was stirred for approximately 15 min at room temperature and initiation of Grignard formation was not observed. The flask was heated using a heat gun to initiate Grignard formation. Once the magnesium turnings had been visibly consumed, the solution of the Grignard reagent was added dropwise to a separate solution of *tert*-butyl 2-(1H-imidazol-1-yl)-2-oxoacetate in THF (25.4 mL) that had been pre-cooled to -78 °C using a dry ice/acetone bath. The resulting mixture was allowed to stir at -78 °C for 1 h prior to being quenched at -78 °C with 10 mL of 1M HCl. Upon warming to room temperature, the reaction mixture was quenched with 40 mL of water, and the aqueous phase was extracted several times with diethyl ether. Purification by silica gel column chromatography delivered *tert*-butyl 2-cyclohexyl-2-oxoacetate **1l** (869 mg, 32% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.90–2.98 (m, 1 H), 1.31–1.91 (m, 19 H).

tert-Butyl 2-Oxo-3-(pyridin-3-yl)butanoate (1m)

The procedure for the preparation of this compound is reported in the literature.[8]

IR (thin film): 2981, 2936, 1723, 1576, 1479, 1455 cm^{-1}.

^{1}H NMR (400 MHz, CDCl3): δ 8.55–8.51 (m, 2 H), 7.55–7.50 (m, 1 H), 7.30–7.25 (m, 1 H), 4.42 (q, *J* = 7.0 Hz, 1 H), 1.48 (d, *J* = 7.1 Hz, 3 H), 1.39 (s, 9 H).

^{13}C NMR (151 MHz, CDCl3): δ 194.3, 160.3, 150.1, 148.8, 135.5, 134.0, 123.7, 84.5, 46.0, 27.6, 16.7.

HRMS: (ESI): calcd for $C_{13}H_{17}NO_3$: ([M+H$^+$]): 236.1287; found: 236.1282.

Nitrones 2; General Procedure[12]

The α-keto ester (0.500 mmol) and *N*-benzylhydroxylamine (1.50 mmol) were combined neat in a flame-dried reaction tube equipped with a stir bar. ^{t}BuOH (1.52 mL) was added and the reaction mixture was sealed and heated at 85 °C for 48 h. Upon complete consumption of the starting α-keto ester, as indicated by TLC (staining with CAM), the reaction mixture was concentrated and purified by silica gel column chromatography.

(*E*)-*N*-Benzyl-1-(*tert*-butoxy)-1-oxo-3-phenylbutan-2-imine Oxide (2a)

Purified by silica gel column chromatography using 80:20 hexanes/EtOAc (94.4 mg, 56% yield).

IR (thin film): 2977, 1709, 1540, 1497, 1456, 1369, 1299, 1254, 1136, 1092, 843, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.46 (m, 2 H), 7.33–7.39 (m, 3 H), 7.20–7.31 (m, 5 H), 5.46 (d, *J* = 13.0 Hz, 1 H), 5.25 (d, *J* = 13.0 Hz, 1 H), 4.82 (q, *J* = 7.1 Hz, 1 H), 1.55 (d, *J* = 7.1 Hz, 3 H), 1.17 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.0, 146.7, 140.8, 133.8, 128.7, 128.6, 128.4, 128.2, 127.6, 126.6, 83.7, 66.8, 37.5, 27.4, 14.0.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{25}NO_3$ [M + H] : 340.1907; found: 340.1916.

(*E*)-*N*-Benzyl-1-(*tert*-butoxy)-3-(4-fluorophenyl)-1-oxobutan-2-imine Oxide (2b)

Purified by silica gel column chromatography using 80:20 hexanes/EtOAc (78.9 mg, 44% yield).

IR (thin film): 2926, 1748, 1733, 1715, 1684, 1558, 1541, 1508, 1497, 1457, 1395, 1371, 1314, 1225, 1136, 846 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.43 (m, 2 H), 7.34–7.36 (m, 3 H), 7.23–7.26 (m, 2 H), 6.96–7.00 (m, 2 H), 5.42 (d, *J* = 13.0 Hz, 1 H), 5.25 (d, *J* = 13.0 Hz, 1 H), 4.76 (q, *J* = 7.0 Hz, 1 H), 1.52 (d, *J* = 7.0 Hz, 3 H), 1.24 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): complex spectrum due to ^{19}F–^{13}C coupling (see the Supporting Information).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{24}FNO_3$ [M + H]: 358.1813; found: 358.1823.

(*E*)-*N*-Benzyl-1-(*tert*-butoxy)-3-(4-chlorophenyl)-1-oxobutan-2-imine Oxide (2c)

Purified by silica gel column chromatography using 80:20 hexanes/EtOAc (89.0 mg, 48% yield).

IR (thin film): 3032, 2978, 2934, 1733, 1716, 1698, 1684, 1647, 1558, 1541, 1507, 1457, 1316, 1137, 845, 705 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.43 (m, 5 H), 7.20–7.27 (m, 4 H), 5.42 (d, *J* = 13.2 Hz, 1 H), 5.27 (d, *J* = 13.2 Hz, 1 H), 4.75 (q, *J* = 7.1 Hz, 1 H), 1.52 (d, *J* = 7.1 Hz, 3 H), 1.25 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.8, 146.0, 139.4, 133.6, 132.4, 129.0, 128.6, 128.6, 128.5, 128.3, 84.0, 66.9, 37.1, 27.5, 14.4.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{24}ClNO_3$ [M + H] : 374.1517; found: 374.1520.

(*E*)-*N*-Benzyl-1-(*tert*-butoxy)-3-(4-bromophenyl)-1-oxobutan-2-imine Oxide (2d)

Prepared using procedure B. Purified via silica gel column chromatography using 80:20 hexanes/ethyl acetate as eluent (137 mg, 66% yield)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40–7.42 (m, 4 H), 7.34–7.35 (m, 3H), 7.15 (d, *J* = 7.7 Hz, 2 H), 5.42 (d, *J* = 13.0 Hz, 1 H), 5.26 (d, *J* = 13.0 Hz, 1 H), 4.72 (q, *J* = 7.1 Hz, 1 H), 1.50 (d, *J* = 7.1 Hz, 3 H), 1.24 (s, 9 H).

(*E*)-*N*-Benzyl-1-(*tert*-butoxy)-3-(2-fluorophenyl)-1-oxobutan-2-imine Oxide (2e)

Purified by silica gel column chromatography using 80:20 hexanes/EtOAc (89.0 mg, 50% yield).

IR (thin film): 3033, 2978, 2935, 2385, 1733, 1716, 1706, 1684, 1653, 1558, 1541, 1457, 1312, 1134, 1113, 844, 758 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.97–7.42 (m, 9 H), 5.38 (d, *J* = 13.1 Hz, 1 H), 5.32 (d, *J* = 13.1 Hz, 1 H), 4.91 (q, *J* = 7.1 Hz, 1 H), 1.56 (d, *J* = 7.1 Hz, 3 H), 1.21 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): complex spectrum due to ^{19}F–^{13}C coupling (see the Supporting Information).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{24}FNO_3$ [M + H] : 358.1813; found: 358.1817.

(*E*)-*N*-Benzyl-1-(*tert*-butoxy)-3-(4-methoxyphenyl)-1-oxobutan-2-imine Oxide (2f)

Purified by silica gel column chromatography using 80:20 hexanes/EtOAc (144.0 mg, 78% yield).

IR (thin film): 2978, 1733, 1716, 1698, 1684, 1653, 1558, 1541, 1507, 1457, 1249, 1137, 1032, 846 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.44 (m, 2 H), 7.32–7.38 (m, 3 H), 7.20 (d, *J* = 8.6 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 5.41 (d, *J* = 13.1 Hz, 1 H), 5.21 (d, *J* = 13.1 Hz, 1 H), 4.74 (q, *J* = 7.1 Hz, 1 H), 3.80 (s, 3 H), 1.52 (d, *J* = 7.1 Hz, 3 H), 1.22 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.1, 158.4, 146.9, 133.7, 132.7, 128.7, 128.6, 128.6, 128.4, 113.6, 83.7, 66.7, 55.3, 36.9, 27.5, 14.4.

HRMS (ESI): *m/z* calcd for $C_{22}H_{27}NO_4$ [M + H] : 370.2013; found: 370.2018.

(*E*)-*N*-Benzyl-1-(*tert*-butoxy)-1-oxo-3-(*p*-tolyl)butan-2-imine Oxide (2g)

Purified by silica gel column chromatography using 80:20 hexanes/EtOAc (128 mg, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.44 (m, 2 H), 7.34–7.37 (m, 3 H), 7.08–7.16 (m, 4 H), 5.42 (d, *J* = 13.0 Hz, 1 H), 5.22 (d, *J* = 13.0 Hz, 1 H), 4.75 (q, *J* = 7.0 Hz, 1 H), 2.30 (s, 3 H), 1.52 (d, *J* = 7.0 Hz, 3 H), 1.19 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.1, 146.8, 137.7, 136.2, 133.8, 128.8, 128.6, 128.6, 128.4, 127.5, 83.6, 66.7, 37.2, 27.4, 20.9, 14.2.

HRMS (ESI): *m/z* calcd for $C_{22}H_{27}NO_3$ [M + H]: 354.2064; found: 354.2070.

(*E*)-*N*-Benzyl-1-(*tert*-butoxy)-1-oxo-3-(*m*-tolyl)butan-2-imine Oxide (2h)

Purified by silica gel column chromatography using 80:20 hexanes/EtOAc (116 mg, 66% yield).

IR (thin film): 3032, 2977, 2934, 1749, 1733, 1716, 1699, 1653, 1558, 1541, 1522, 1507, 1457, 1315, 1135, 841, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.48 (m, 2 H), 7.35–7.40 (m, 3 H), 7.18–7.22 (m, 1 H), 7.04–7.09 (m, 3 H), 5.48 (d, *J* = 13.0 Hz, 1 H), 5.27 (d, *J* = 13.0 Hz, 1 H), 4.81 (q, *J* = 7.3 Hz, 1 H), 2.33 (s, 3 H), 1.55 (d, *J* = 7.3 Hz, 3 H), 1.20 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.0, 150.0, 146.9, 140.7, 137.7, 133.8, 128.7, 128.6, 128.4, 128.4, 128.1, 127.3, 124.7, 83.6, 66.7, 37.5, 27.4, 21.4, 14.1.

HRMS (ESI): *m/z* calcd for $C_{22}H_{27}NO_3$ [M + H]: 354.2064; found: 354.2071.

(*E*)-*N*-Benzyl-1-(*tert*-butoxy)-1-oxo-4-phenyl-3-(4-(trifluoromethyl)phenyl)butan-2-imine Oxide (2i)

Purified by silica gel column chromatography using 80:20 hexanes/EtOAc (260 mg, 50% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.3 Hz, 2 H), 7.46 (d, *J* = 8.3 Hz, 2 H), 7.29–7.34 (m, 3 H), 7.25–7.26 (m, 2 H), 7.16–7.20 (m, 3 H), 7.10–7.12 (m, 2 H), 5.39 (d, *J* = 12.8 Hz, 1 H), 5.28 (d, *J* = 12.8 Hz, 1 H), 5.01–5.04 (app t, *J* = 8.1 Hz, 1 H), 3.51 (dd, *J* = 8.8, 13.6 Hz, 1 H), 3.22 (dd, *J* = 7.4, 13.7 Hz, 1 H), 1.32 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): complex spectrum due to ^{19}F–^{13}C coupling (see the Supporting Information).

HRMS (ESI): *m/z* calcd for $C_{28}H_{28}F_3NO_3$ [M + H] : 484.2094; found: 484.2105.

(*E*)-N-Benzyl-1-(*tert*-butoxy)-1-oxo-3-phenylpentan-2-imine Oxide (2j)

Prepared using procedure B. Purified via silica gel column chromatography using 80:20 hexanes/ethyl acetate as eluent (106 mg, 60% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.20–7.40 (m, 10 H), 5.35 (d, *J* = 13.0 Hz, 1 H), 5.20 (d, *J* = 13.0 Hz, 1 H), 4.56–4.59 (dd or app t, *J* = 7.6 Hz, 7.6 Hz, 1 H), 1.98–2.08 (m, 2 H), 1.31 (s, 9 H), 0.95 (t, *J* = 7.3 Hz, 3 H).

(*E*)-*N*-Benzyl-1-(*tert*-butoxy)-1-oxo-4-phenylbutan-2-imine Oxide (2k)

Purified by silica gel column chromatography using 80:20 hexanes/EtOAc (146 mg, 86% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48–7.49 (m, 2 H), 7.32–7.40 (m, 3 H), 7.21–7.24 (m, 2 H), 7.15–7.18 (m, 1 H), 7.10–7.12 (m, 2 H), 5.63 (s, 2 H), 2.96–2.99 (m, 2 H), 2.83–2.86 (m, 2 H), 1.40 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.6, 141.9, 141.1, 134.2, 128.9, 128.5, 128.5, 128.4, 128.3, 126.0, 83.0, 66.9, 31.2, 30.3, 27.8.

HRMS (ESI): *m/z* calcd for $C_{21}H_{25}NO_3$ [M + Na]: 362.1732; found: 362.1722.

(*E*)-N-Benzyl-2-(*tert*-butoxy)-1-cyclohexyl-2-oxoethan-1-imine Oxide (2l)

Prepared using procedure B. Purified via silica gel column chromatography using 80:20 hexanes/ethyl acetate as eluent (103 mg, 65% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.39 (m, 2 H), 7.29–7.33 (m, 3 H), 3.18–3.26 (m, 1 H), 1.29–1.82 (m, 19 H).

(*E*)-N-Benzyl-1-(*tert*-butoxy)-1-oxo-3-(pyridin-3-yl)butan-2-imine Oxide (2m)

Prepared using procedure B. Purified via silica gel column chromatography using gradient elution from 40% to 60% ethyl acetate in hexanes as eluent (129 mg, 76% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.50 (s, 1 H), 8.41–8.42 (m, 1 H), 7.54–7.56 (m, 1 H), 7.29–7.35 (m, 5 H), 5.37 (d, *J* = 13.0 Hz, 1 H), 5.27 (m, *J* = 13.0 Hz, 1 H), 4.74 (q, *J* = 6.8 Hz, 1 H), 1.52 (d, *J* = 6.8 Hz, 1 H), 1.23 (s, 9 H).

α-Imino Esters 3 via Multihetero-Cope Rearrangement; General Procedure

Activated 4 Å molecular sieves were added to a 15-mL flame-dried round-bottomed flask. DMAP (0.2 equiv) and Proton-sponge® (2.5 equiv) were added to the flask. The nitrone **2** (0.15 mmol) was then added in MTBE (1.50 mL) and the resulting suspension was cooled in an ice bath. The aroyl chloride (2.0 equiv) was added slowly in MTBE (1.0 mL), and the mixture was gradually allowed to warm to rt. The reaction mixture was stirred for 4 h. Upon complete consumption of the nitrone, as indicated by TLC (staining with CAM), the crude mixture was passed through a pad of Celite using diethyl ether to rinse. The crude residue was purified by silica gel column chromatography, unless otherwise noted.

(*Z*)-3-(Benzylimino)-4-(*tert*-butoxy)-4-oxo-2-phenylbutan-2-yl Benzoate (3a)

Purified by silica gel column chromatography using 5% and then 10% EtOAc/hexane (57.6 mg, 86% yield).

IR (thin film): 2977, 1709, 1540, 1497, 1456, 1369, 1299, 1254, 1136, 1092, 843, 700 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.19–8.20 (m, 2 H), 7.60–7.61 (m, 3 H), 7.50–7.52 (m, 2 H), 7.36–7.42 (m, 6 H), 7.28–7.34 (m, 2 H), 4.84 (d, *J* = 15.0 Hz, 1 H), 4.71 (d, *J* = 15.0 Hz, 1 H), 2.23 (s, 3 H), 1.24 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.7, 164.4, 162.7, 141.7, 138.7, 133.1, 130.8, 129.7, 128.4, 128.3, 128.1, 127.8, 127.5, 126.9, 125.2, 85.5, 83.5, 57.4, 27.8, 25.5.

HRMS (ESI): *m/z* calcd for $C_{28}H_{29}NO_4$ [M + H] : 444.2169; found: 444.2161.

(*Z*)-3-(Benzylimino)-4-(*tert*-butoxy)-2-(4-fluorophenyl)-4-oxobutan-2-yl Benzoate (3b)

Purified by silica gel column chromatography using 5% and then 10% EtOAc/hexane (59.1 mg, 85% yield).

IR (thin film): 2926, 1748, 1733, 1715, 1684, 1558, 1541, 1508, 1497, 1457, 1395, 1371, 1314, 1225, 1136, 846 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.15–8.16 (m, 2 H), 7.60–7.63 (m, 1 H), 7.54–7.57 (m, 2 H), 7.49–7.51 (m, 2 H), 7.35–7.38 (m, 4 H), 7.27–7.31 (m, 1 H), 7.06–7.09 (m, 2 H), 4.81 (d, *J* = 14.9 Hz, 1 H), 4.68 (d, *J* = 14.9 Hz, 1 H), 2.20 (s, 3 H), 1.26 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): complex spectrum due to ^{19}F–^{13}C coupling (see the Supporting Information).

HRMS (ESI): *m*/*z* calcd for $C_{28}H_{28}FNO_4$ [M + H]: 462.2075; found: 462.2070.

(*Z*)-3-(Benzylimino)-4-(*tert*-butoxy)-2-(4-chlorophenyl)-4-oxobutan-2-yl Benzoate (3c)

Purified by silica gel column chromatography using 5% and then 10% EtOAc/hexane (51.9 mg, 72% yield).

IR (thin film): 3032, 2978, 2934, 1733, 1716, 1698, 1684, 1647, 1558, 1541, 1507, 1457, 1316, 1137, 845, 705 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.14–8.16 (m, 2 H), 7.61–7.63 (m, 1 H), 7.50–7.53 (m, 4 H), 7.35–7.39 (m, 6 H), 7.28–7.30 (m, 1 H), 4.82 (d, *J* = 14.9 Hz, 1 H), 4.68 (d, *J* = 14.9 Hz, 1 H), 2.19 (s, 3 H), 1.27 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.5, 164.1, 162.6, 140.4, 138.5, 133.4, 133.3, 130.5, 129.7, 128.5, 128.4, 128.3, 127.8, 127.0, 126.7, 85.1, 83.8, 77.2, 57.4, 27.8, 25.4.

HRMS (ESI): *m*/*z* calcd for $C_{28}H_{28}ClNO_4$ [M + H]: 478.1780; found: 478.1777.

(*Z*)-3-(benzylimino)-4-(*tert*-butoxy)-2-(4-bromophenyl)-4-oxobutan-2-yl benzoate (3d)

Prepared using procedure C. Purified via silica gel column chromatography using 5% and then 10% ethyl acetate/hexane as eluent (71.1 mg, 91% yield).

^1H NMR ($CDCl_3$, 600 MHz): δ 8.15 (d, *J* = 8.2 Hz, 2H), 7.61–7.63 (m, 1H), 7.49–7.52 (m, 4H), 7.45–7.47 (m, 2 H), 7.35–7.39 (m, 4 H), 7.28–7.30 (m, 1 H), 4.82 (d, *J* = 14.9 Hz, 1 H), 4.68 (d, *J* = 14.9 Hz, 1 H), 2.19 (s, 3 H), 1.27 (9 H).

^{13}C NMR ($CDCl_3$, 150 MHz): 164.5, 164.0, 162.6, 141.0, 138.5, 133.3, 131.3, 130.5, 129.7, 128.5, 128.4, 127.8, 127.0, 127.0, 121.7, 85.1, 83.8, 57.4, 27.8, 25.4.

(*Z*)-3-(Benzylimino)-4-(*tert*-butoxy)-2-(2-fluorophenyl)-4-oxobutan-2-yl Benzoate (3e)

Purified by silica gel column chromatography using 5% and then 10% EtOAc/hexane (60.5 mg, 87% yield).

IR (thin film): 3033, 2978, 2935, 2385, 1733, 1716, 1706, 1684, 1653, 1558, 1541, 1457, 1312, 1134, 1113, 844, 758 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.5 Hz, 2 H), 7.65–7.69 (m, 1 H), 7.55–7.59 (m, 1 H), 7.43–7.47 (m, 2 H), 7.26–7.35 (m, 6 H), 7.17–7.20 (m, 1 H), 7.00–7.06 (m, 1 H), 4.70–4.79 (m, 2 H), 2.36 (s, 3 H), 1.37 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): complex spectrum due to ^{19}F–^{13}C coupling (see the Supporting Information).

HRMS (ESI): *m*/*z* calcd for $C_{28}H_{28}FNO_4$ [M + H]: 462.2075; found: 462.2075.

(*Z*)-3-(Benzylimino)-4-(*tert*-butoxy)-2-(4-methoxyphenyl)-4-oxobutan-2-yl Benzoate (3f)

Purified by silica gel column chromatography using 80:20 hexane/EtOAc (52.0 mg, 73% yield).

IR (thin film): 2978, 1733, 1716, 1698, 1684, 1653, 1558, 1541, 1507, 1457, 1249, 1137, 1032, 846 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.17 (m, 2 H), 7.58–7.61 (m, 1 H), 7.46–7.51 (m, 4 H), 7.35–7.36 (m, 4 H), 7.26–7.30 (m, 1 H), 6.92 (d, *J* = 8.9 Hz, 2 H), 4.80 (d, *J* = 14.8 Hz, 1 H), 4.68 (d, *J* = 14.8 Hz, 1 H), 3.82 (s, 3 H), 2.21 (s, 3 H), 1.26 (s, 9 H).

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{31}NO_5$ [M + H]: 474.2275; found: 474.2264.

(*Z*)-3-(Benzylimino)-4-(*tert*-butoxy)-4-oxo-2-(*p*-tolyl)butan-2-yl Benzoate (3g)

Purified by silica gel column chromatography using 2.55% and then 5% EtOAc/hexane (65.2 mg, 95% yield).

IR (thin film): 3062, 3030, 2979, 2935, 2870, 1731, 1453 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.16–8.17 (m, 2 H), 7.59–7.61 (m, 1 H), 7.46–7.50 (m, 4 H), 7.35–7.38 (m, 4 H), 7.27–7.29 (m, 1 H), 7.19–7.20 (m, 2 H), 4.80 (d, *J* = 14.9 Hz, 1 H), 4.68 (d, *J* = 14.9 Hz, 1 H), 2.36 (s, 3 H), 2.20 (s, 3 H), 1.24 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.7, 164.6, 162.9, 138.8, 137.2, 133.1, 130.9, 129.7, 128.9, 128.4, 128.3, 127.8, 126.8, 125.1, 85.5, 83.5, 57.4, 27.8, 25.4, 21.1.

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{31}NO_4$ [M + H]: 458.2326; found: 458.2323.

(*Z*)-3-(Benzylimino)-4-(*tert*-butoxy)-4-oxo-2-(*m*-tolyl)butan-2-yl Benzoate (3h)

Purified by silica gel column chromatography using 5% and then 10% EtOAc/hexane (57.2 mg, 83% yield).

IR (thin film): 3032, 2977, 2934, 1749, 1733, 1716, 1699, 1653, 1558, 1541, 1522, 1507, 1457, 1315, 1135, 841, 702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.17–8.19 (m, 2 H), 7.59–7.62 (m, 1 H), 7.48–7.52 (m, 2 H), 7.41–7.44 (m, 1 H), 7.34–7.37 (m, 5 H), 7.26–7.30 (m, 2 H), 7.12–7.14 (m, 1 H), 4.82 (d, *J* = 14.8 Hz, 1 H), 4.70 (d, *J* = 14.8 Hz, 1 H), 2.36 (s, 3 H), 2.21 (s, 3 H), 1.24 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.7, 164.5, 162.8, 141.6, 138.7, 137.6, 133.1, 130.9, 129.7, 128.4, 128.3, 128.3, 128.0, 127.9, 126.9, 126.0, 122.2, 85.5, 83.4, 57.5, 27.8, 25.4, 21.7.

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{31}NO_4$ [M + H]: 458.2326; found: 458.2316.

(*Z*)-3-(Benzylimino)-4-(*tert*-butoxy)-4-oxo-1-phenyl-2-(4-(trifluoromethyl)phenyl)butan-2-yl Benzoate (3i)

Purified by silica gel column chromatography using 5% and then 10% EtOAc/hexane (67.9 mg, 77% yield).

IR (thin film): 3064, 3032, 2979, 2933, 1733, 1327 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.00–8.01 (m, 2 H), 7.54–7.62 (m, 5 H), 7.45–7.48 (m, 4 H), 7.41–7.43 (m, 2 H), 7.32–7.35 (m, 1 H), 7.04–7.07 (m, 1 H), 6.95–6.98 (m, 2 H), 6.60–6.61 (m, 2 H), 4.94 (d, *J* = 14.8 Hz, 1 H), 4.76 (d, *J* = 14.8 Hz, 1 H), 4.42 (d, *J* = 14.6 Hz, 1 H), 3.73 (d, *J* = 14.6 Hz, 1 H), 1.15 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): complex spectrum due to ^{19}F–^{13}C coupling (see the Supporting Information).

HRMS (ESI): *m*/*z* calcd for $C_{35}H_{32}F_3NO_4$ [M + H]: 588.2356; found: 588.2352.

(*Z*)-2-(Benzylimino)-1-(*tert*-butoxy)-1-oxo-3-phenylpentan-3-yl Benzoate (3j)

Purified by silica gel column chromatography using 5% EtOAc/hexane (46.7 mg, 68% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 7.5 Hz, 2 H), 7.59–7.64 (m, 3 H), 7.51 (t, *J* = 7.5 Hz, 2 H), 7.36–7.42 (m, 6 H), 7.28–7.34 (m, 2 H), 4.83 (d, *J* = 14.9 Hz, 1 H), 4.68 (d, *J* = 14.9 Hz, 1 H), 3.14 (dq, *J* = 7.4, 14.8 Hz, 1 H), 2.54 (dq, *J* = 7.4, 14.8 Hz, 1 H), 1.21 (s, 9 H), 0.73 (app t, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.6, 164.4, 162.7, 139.9, 138.7, 133.2, 130.6, 129.7, 128.5, 128.3, 128.0, 127.9, 127.4, 126.9, 125.5, 88.1, 83.3, 57.4, 29.1, 27.7, 6.96.

(*Z*)-3-(Benzylimino)-4-(*tert*-butoxy)-4-oxo-2-phenylbutan-2-yl 4-Methylbenzoate (3n)

Purified by silica gel column chromatography using 20% EtOAc/hexane (63.8 mg, 93% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.2 Hz, 2 H), 7.60–7.61 (m, 2 H), 7.28–7.41 (m, 10 H), 4.84 (d, *J* = 15 Hz, 1 H), 4.70 (d, *J* = 15.0 Hz, 1 H), 2.45 (s, 3 H), 2.22 (s, 3 H), 1.24 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): 164.7, 164.5, 162.7, 143.8, 141.8, 138.7, 129.7, 129.1, 128.3, 128.1, 128.0, 127.8, 127.4, 126.8, 125.2, 85.3, 83.4, 57.3, 27.8, 25.5, 21.7.

(*Z*)-3-(Benzylimino)-4-(*tert*-butoxy)-4-oxo-2-phenylbutan-2-yl 3-Chlorobenzoate (3o)

Purified by silica gel column chromatography using 20% EtOAc/hexane (68.8 mg, 96% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (m, 1 H), 8.05–8.06 (m, 1 H), 7.57–7.59 (m, 3 H), 7.28–7.46 (m, 9 H), 4.82 (d, *J* = 14.9 Hz, 1 H), 4.70 (d, *J* = 14.9 Hz, 1 H), 2.23 (s, 3 H), 1.27 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.1, 163.5, 162.7, 141.3, 138.6, 134.6, 133.1, 132.5, 129.8, 129.7, 128.3, 128.2, 127.8, 127.8, 127.7, 126.9, 125.2, 86.0, 83.7, 57.4, 27.8, 25.2.

(*Z*)-3-(Benzylimino)-4-(*tert*-butoxy)-4-oxo-2-phenylbutan-2-yl 2-Bromobenzoate (3p)

Purified by silica gel column chromatography using 20% EtOAc/hexane (68.2 mg, 87% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89–7.92 (m, 1 H), 7.68–7.69 (m, 1 H), 7.57–7.59 (m, 2 H), 7.27–7.42 (m, 10 H), 4.83 (d, *J* = 15.0 Hz, 1 H), 4.70 (d, *J* = 15.0 Hz, 1 H), 2.26 (s, 3 H), 1.26 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): 164.3, 164.1, 162.6, 141.3, 138.7, 134.2, 132.9, 132.4, 131.3, 128.3, 128.1, 127.8, 127.5, 127.1, 126.9, 125.4, 121.4, 86.3, 83.5, 57.4, 27.8, 25.1.

***syn*-2-(Benzylamino)-3-(4-methoxyphenyl)butane-1,3-diol (4f) via $LiAlH_4$ Reduction; Typical Procedure**

α-Imino ester **3f** (248 mg, 0.52 mmol) was dissolved in THF (3.50 mL). The resulting solution was cooled in an ice bath, and $LiAlH_4$ (2 M in THF, 2.10 mL, 8.0 equiv) was slowly added. The reaction mixture was stirred for 12 h, and then quenched with saturated aqueous sodium sulfate until gas evolution had ceased. The resulting mixture was passed through a plug of Celite using EtOAc to rinse. The resulting product was purified by silica gel column chromatography using 30% and then 50% EtOAc/hexanes to give the major diastereomer of **4f** (87.5 mg isolated, 56% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.35 (m, 7 H), 6.86–6.88 (m, 2 H), 3.95 (d, *J* = 13.0 Hz, 1 H), 3.88 (d, *J* = 13.0 Hz, 1 H), 3.80 (s, 3 H), 3.50 (dd, *J* = 4.4, 11.5 Hz, 1 H), 3.42 (dd, *J* = 3.4, 11.5 Hz, 1 H), 2.75–2.77 (m, 1 H), 1.59 (s, 3 H).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{23}NO_3$ [M + H]: 302.1756; found: 302.1743.

***syn*-2-(Benzylamino)-3-phenylbutane-1,3-diol (4a)**

α-Imino ester **3a** (146 mg, 0.329 mmol) was used as starting material, to give the major diastereomer of **4a** (51.8 mg isolated, 58% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.39–7.40 (m, 2 H), 7.33–7.36 (m, 6 H), 7.25–7.30 (m, 2 H), 3.96 (d, *J* = 13.0 Hz, 1 H), 3.88 (d, *J* = 13.0 Hz, 1 H), 3.48 (dd, *J* = 4.1, 11.5 Hz, 1 H), 3.37 (dd, *J* = 3.3, 11.5 Hz, 1 H), 2.78–2.80 (m, 1 H), 1.61 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 145.8, 140.0, 128.5, 128.3, 128.2, 127.2, 126.8, 124.7, 77.1, 64.9, 61.1, 53.4, 27.9.

(±)-(2*R*,3*S*)-3-(Benzylamino)-4-((*tert*-butyldimethylsilyl)oxy)-2-(4-methoxyphenyl)butan-2-ol ((±)-S1)

A flame-dried vial was cooled under N_2, and charged with alcohol (±)-**4f** (34.0 mg, 0.113 mmol, 1 equiv), imidazole (23.0 mg, 0.338 mmol, 3 equiv), and CH_2Cl_2 (1 mL). The solution was cooled to 0 °C, and TBSCl (37.4 mg, 0.248 mmol, 2.2 equiv) was added. The reaction mixture was allowed to warm to rt slowly overnight, and stirred for a total of 16 h. The reaction mixture was passed through a plug of silica gel, and the plug was washed with EtOAc (3 × 2 mL), then concentrated. The crude product was purified by silica gel column chromatography (EtOAc/hexanes, 10:90), which afforded (±)-**S1** (39.0 mg, 83% yield) as a clear and colorless liquid.

R_f = 0.2 (EtOAc/hexane, 10:90).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.24–7.37 (m, 7 H), 6.84 (d, *J* = 7.3 Hz, 2 H), 3.95 (d, *J* = 13.0 Hz, 1 H), 3.75–3.82 (m, 4 H), 3.57 (dd, *J* = 10.4, 3.9 Hz, 1 H), 3.34 (app d, *J* = 8.1 Hz, 1 H), 2.76 (br s, 1 H), 1.59 (s, 3 H), 0.86 (s, 9 H), –0.01 (s, 3 H), –0.05 (s, 3 H).

(±)-(4*S*,5*R*)-3-Benzyl-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(4-methoxyphenyl)-5-methyloxazolidin-2-one ((±)-5f)

A flame-dried vial was cooled under N_2, and charged with amino alcohol (±)-**S1** (34.0 mg, 0.0828 mmol, 1 equiv), THF (0.5 mL), and Et_3N (34 μL, 0.245 mmol, 3 equiv). The solution was cooled to 0 °C, and a solution of triphosgene (29.1 mg, 0.0982 mmol, 1.2 equiv) in THF (1 mL) was added dropwise. The reaction mixture was allowed to warm to rt slowly overnight, and stirred for a total of 16 h. The reaction mixture was diluted with saturated aqueous ammonium chloride (1 mL), and stirred for 30 min. The reaction mixture was added to a separatory funnel, and diluted with CH_2Cl_2 (30 mL) and saturated aqueous ammonium chloride (30 mL). The layers were separated, and the organic layer was collected. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (EtOAc/hexanes, 10:90 to 15:85), which afforded (±)-**5f** (32.9 mg, 91% yield) as a clear and colorless liquid.

R_f = 0.15 (EtOAc/hexane, 10:90).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34–7.39 (m, 2 H), 7.30–7.35 (m, 3 H), 7.23–7.28 (m, 2 H), 6.85 (d, J = 8.8 Hz, 2 H), 4.98 (d, J = 15.0 Hz, 1 H), 4.09 (d, J = 15.0 Hz, 1 H), 3.80 (s, 3 H), 3.39 (app t, J = 4.1 Hz, 1 H), 3.25 (app qd, J = 11.0, 4.2 Hz, 2 H), 1.63 (s, 3 H), 0.80 (s, 9 H), –0.15 (s, 3 H), –0.26 (s, 3 H).

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Supporting Information

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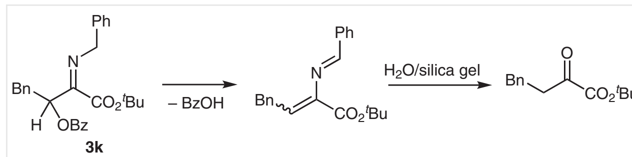

Scheme 4

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