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

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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 LiAlH₄ 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-oxygenamine 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-oxygenamines 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-alkyl-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-oxygenamine 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-oxygenamines. 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactants</th>
<th>Baseb</th>
<th>Catalyst</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>Yield (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1d</td>
<td>1a/A</td>
<td>none</td>
<td>none</td>
<td>55</td>
<td>DMSO (0.375 M)</td>
<td>0</td>
</tr>
<tr>
<td>2f</td>
<td>2a/B</td>
<td>Et₃N</td>
<td>DMAP</td>
<td>0; 23</td>
<td>MTBE (0.06 M)</td>
<td>48</td>
</tr>
<tr>
<td>3n</td>
<td>2a/B</td>
<td>PS</td>
<td>DMAP</td>
<td>0; 23</td>
<td>MTBE (0.06 M)</td>
<td>86</td>
</tr>
<tr>
<td>4n</td>
<td>2a/B</td>
<td>PS</td>
<td>DMAP</td>
<td>0; 23</td>
<td>MTBE (0.06 M)</td>
<td>63</td>
</tr>
</tbody>
</table>

a All reactions run using 0.15 mmol of 1a or 2a.
b PS = Proton-spongec.
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 Et₃N 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 1H 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 α-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.
In summary, we have developed a sequential benzylation–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 LiAlH₄ 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. H and ¹³C NMR spectra were obtained on a Bruker DRX 600 (¹H, 600 MHz; ¹³C, 150 MHz), Bruker 500 (¹H, 500 MHz; ¹³C, 125 MHz), or Bruker DRX 400 (¹H, 400 MHz; ¹³C, 100 MHz) spectrometer. HRMS 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·min⁻¹. The solvents were degassed using an on-line membrane degasser (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·min⁻¹, and nebulizing gas pressure 15 psi. Detection was carried out considering a mass range of 100–1500 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·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 ¹²C and ¹³C/mol 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 KMnO₄ solution, followed by heating. Flash chromatography was performed under positive nitrogen pressure using SiliaFlash-P60 silica gel (40–63 μm) purchased from SiliCycle.

Et₃N was purified and dried by passing through a column of activated alumina. DMAP and BuOH were purchased from Sigma-Aldrich 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-

Feature

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. 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 aryl 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 LiAlH₄ 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.

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

In summary, we have developed a sequential benzylation–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 LiAlH₄ 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.
procedures for the preparation of tert-butyl 2-oxo-4-phenylbutanoate (1k)\(^1\) and tert-butyl 2-oxo-4-phenyl-3-(4-(trifluoromethyl)phenyl)-butanoate (1i)\(^2\) 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

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

tert-Butyl \(\alpha\)-Keto Esters 1; General Procedure
Step 1: The ethyl 2-oxo-3-arylbutanoate (4.46 mmol), prepared in two steps via a literature method,\(^1\) 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\(_2\)Cl\(_2\) (3 × 15 mL). The combined organic layers were dried over MgSO\(_4\). Filtration through a plug of cotton and concentration delivered the corresponding \(\alpha\)-keto acid which was carried on without purification.

Step 2: The crude \(\alpha\)-keto acid from step 1 was dissolved in CH\(_2\)Cl\(_2\) (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: \(^1\)BuOH (1.27 mL, 13.4 mmol, 3.0 equiv) and pyridine (719 \(\mu\)L, 8.92 mmol, 2.0 equiv) were dissolved in CH\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\) (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).
acetate/hexanes (531 mg, 48% yield).

**13C NMR (150 MHz, CDCl 3):**
\[ \delta = 195.2, 161.0, 138.1, 128.9, 122.5, 127.5, 83.9, 48.8, 27.6, 16.6 \]

HRMS (ESI): m/z calc for C_{13}H_{20}O_2 [M + Na]: 275.1154; found: 275.1148.

**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.

**1H NMR (400 MHz, CDCl 3):**
\[ \delta = 7.41–7.48 (m, 1 H), 7.05–7.11 (m, 3 H), 6.99–7.01 (m, 2 H), 4.31 (q, J = 7.00 Hz, 1 H), 2.32 (s, 3 H), 1.42 (d, J = 7.30 Hz, 3 H), 1.34 (s, 9 H) \]

HRMS (ESI): m/z calc for C_{13}H_{20}O_2 [M + Na]: 275.1154; found: 275.1148.

**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.

**1H NMR (400 MHz, CDCl 3):**
\[ \delta = 7.31–7.33 (m, 1 H), 7.06–7.08 (m, 1 H), 6.99–7.01 (m, 2 H), 4.31 (q, J = 7.00 Hz, 1 H), 2.32 (s, 3 H), 1.43 (d, J = 7.00 Hz, 3 H), 1.34 (s, 9 H) \]

HRMS (ESI): m/z calc for C_{13}H_{19}ClO_2 [M + Na]: 271.0764; found: 271.0756.

**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 (331 mg, 48% yield).

**1H NMR (CDCl 3, 400 MHz):**
\[ \delta = 7.46 (d, J = 8.40 Hz, 2 H), 7.09 (d, J = 8.40 Hz, 2 H), 4.34 (q, J = 7.00 Hz, 1 H), 1.42 (d, J = 7.00 Hz, 3 H), 1.38 (s, 9 H) \]

HRMS (ESI): m/z calc for C_{13}H_{19}BrO_2 [M + Na]: 271.1304; found: 271.1303.
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-oxooctoate 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-oxooctoate 11 (869 mg, 32% yield).

1H NMR (CDCl3, 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.

IR (thin film): 2977, 1709, 1540, 1497, 1456, 1369, 1299, 1254, 1136, 1032, 846 cm–1.

(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.

1H NMR (400 MHz, CDCl3): δ 7.30–7.33 (m, 2 H), 7.34–7.39 (m, 3 H), 7.39–7.42 (m, 4 H), 7.34–7.35 (m, 3 H), 7.40–7.42 (m, 9 H), 5.38 (d, J = 7.1 Hz, 1 H), 1.55 (d, J = 7.1 Hz, 3 H), 1.17 (s, 9 H).

13C NMR (150 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.


(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/EtOAc as eluent (137 mg, 66% yield).

IR (thin film): 3032, 2978, 2934, 236.1282.

1H NMR (CDCl3, 400 MHz):

δ 7.40–7.42 (m, 2 H), 7.43–7.39 (m, 3 H), 7.15 (d, J = 7.7 Hz, 2 H), 5.42 (d, J = 13.1 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).

13C NMR (150 MHz, CDCl3): δ 161.8, 146.0, 139.4, 133.6, 132.4, 129.0, 128.6, 128.5, 128.3, 84.0, 66.9, 37.1, 27.5, 14.4.

HRMS (ESI): m/z calcd for C21H24ClNO3 [M + H]: 374.1517; found: 374.1520.

*(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).

HRMS (ESI): m/z calcd for C21H24FNO3 [M + H]: 358.1813; found: 358.1813.

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

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

HRMS (ESI): m/z calcd for C21H24ClNO3 [M + H]: 374.1517; found: 374.1520.
**Synthesis**
S. L. Bartlett et al.

HRMS (ESI): m/z calcld for C_{22}H_{27}NO_{4} [M + H] : 370.2013; found: 370.198.

(E)-N-Benzyl-1-(tert-butoxy)-1-oxo-3-(p-toly)butan-2-imide Oxide (2g)

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

1H 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).

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

HRMS (ESI): m/z calcld for C_{22}H_{27}NO_{3} [M + H]: 354.2064; found: 354.2070.

(E)-N-Benzyl-1-(tert-butoxy)-1-oxo-3-(m-toly)butan-2-imide Oxide (2h)

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).

1H 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-4-phenylbutan-2-imino Oxide Oxide (2k)

1H 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 nitron 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 (1.50 mL) and the resulting suspension was cooled in an ice bath. The aroyl chloride (2.0 equiv) was added slowly in MTBE (1.50 mL) and the resulting suspension was cooled in an ice bath.

(E)-N-Benzyl-1-(tert-butoxy)-1-oxo-4-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): 3032, 2977, 2934, 1749, 1733, 1716, 1699, 1653, 1558, 1541, 1522, 1507, 1457, 1315, 1135, 841, 702 cm\(^{-1}\).

(E)-N-Benzyl-1-(tert-butoxy)-1-oxo-4-phenylbutan-2-yl Benzoate (3a)

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

1H NMR (CDCl_3, 500 MHz): δ = 6.94 (s, 1 H), 7.28–7.32 (m, 4 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).

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

HRMS (ESI): m/z calcld for C_{28}H_{30}F_{3}NO_{3} [M + H]: 484.2105; found: 484.2105.

(Z)-3-(Benzyllimino)-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\(^{-1}\).

(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).

1H 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).

13C NMR (150 MHz, CDCl_3): δ = 150.5, 149.0, 140.6, 138.3, 130.0, 129.7, 128.7, 128.4, 127.5, 126.9, 125.2, 85.5, 83.5, 75.4, 27.8, 25.5.

HRMS (ESI): m/z calcld for C_{32}H_{34}NO_{5} + Na [M + Na]: 444.2169; found: 444.2161.
(Z)-3-(Benzylic)-4-(tert-butoxy)-2-(4-fluorophenyl)-4-oxo-but-2-yn-1-yl benzoate (3b)

Purified by silica gel column chromatography using 5% and then 10% EtOAc/hexane (51.9 mg, 85% yield).

IR (thin film): 2926, 1748, 1733, 1715, 1684, 1597, 1457, 1395, 1371, 1314, 1225, 1136, 846 cm⁻¹.

1H NMR (600 MHz, CDCl₃): 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).

13C NMR (150 MHz, CDCl₃): complex spectrum due to ¹⁹F-¹³C coupling (see the Supporting Information).

HRMS (ESI): m/z calcd for C₂₆H₂₈NO₃ [M + H]: 462.2075; found: 462.2070.

(Z)-3-(Benzylic)-4-(tert-butoxy)-2-(4-chlorophenyl)-4-oxo-but-2-yn-1-yl benzoate (3c)

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

IR (thin film): 2932, 2978, 2934, 1733, 1716, 1698, 1684, 1647, 1558, 1541, 1507, 1457, 1316, 1137, 845, 705 cm⁻¹.

1H NMR (600 MHz, CDCl₃): 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).

13C NMR (150 MHz, CDCl₃): 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 C₂₆H₂₈ClNO₃ [M + H]: 478.1777; found: 478.1777.

(Z)-3-(Benzylic)-4-(tert-butoxy)-2-(4-bromophenyl)-4-oxo-but-2-yn-1-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 (CDCl₃, 600 MHz): δ = 8.15 (d, J = 8.2 Hz, 2 H), 7.61–7.63 (m, 1 H), 7.49–7.52 (m, 4 H), 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 (s, 9 H).

13C NMR (CDCl₃, 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, 77.2, 57.4, 27.8, 25.4.

HRMS (ESI): m/z calcd for C₂₆H₂₈BrNO₃ [M + H]: 548.2326; found: 548.2323.

(Z)-3-(Benzylic)-4-(tert-butoxy)-2-(4-methoxyphenyl)-4-oxo-but-2-yn-1-yl benzoate (3f)

Purified by silica gel column chromatography using 5% and then 10% EtOAc/hexane (65.2 mg, 95% yield).

IR (thin film): 3062, 3030, 2979, 2935, 2870, 1731, 1453 cm⁻¹.

1H NMR (600 MHz, CDCl₃): 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), 1.24 (s, 9 H).

13C NMR (150 MHz, CDCl₃): 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 C₂₆H₂₈NO₃ [M + H]: 458.2326; found: 458.2326.

(Z)-3-(Benzylic)-4-(tert-butoxy)-4-oxo-2-(m-toly)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): 3033, 2977, 2934, 1749, 1733, 1716, 1699, 1653, 1558, 1541, 1522, 1507, 1457, 1315, 1135, 841, 702 cm⁻¹.

1H NMR (400 MHz, CDCl₃): 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).

13C NMR (150 MHz, CDCl₃): δ = 164.7, 164.5, 162.8, 141.6, 138.7, 137.6, 133.1, 130.9, 129.7, 128.4, 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 C₂₆H₂₈NO₃ [M + H]: 458.2326; found: 458.2316.
Purified by silica gel column chromatography using 20% EtOAc/hexanes (63.8 mg, 93% yield).

Methylbenzoate (3n) (68.8 mg, 96% yield).

Purified by silica gel column chromatography using 20% EtOAc/hexane (46.7 mg, 68% yield).

1H NMR (500 MHz, CDCl3): 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 calcld for C18H23NO3 [M + H]: 302.1756; found: 302.1743.

syn-2-(Benzylinolo)-3-phenylbutane-1,3-diol (4α)

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

1H NMR (500 MHz, CDCl3): 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).

13C NMR (150 MHz, CDCl3): 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.

HRMS (ESI): m/z calcld for C18H23NO3 [M + H]: 302.1756; found: 302.1743.

(2R,2S,3S,5R)-3-Benzyl-4-((tert-butyldimethylsilyl)oxy)-5-(4-methoxyphenyl)oxazolidin-2-one (4f) via LiAlH₄ Reduction; Typical Procedure

A flame-dried vial was cooled under N₂, and charged with alcohol (±)-3-bromo-4-((tert-butyldimethylsilyl)oxy)-5-(4-methoxyphenyl)oxazolidin-2-one (±)-S1 (0.245 mmol, 3 equiv) and CH₂Cl₂ (1 mL). The solution was cooled to 0 °C, and TBSCI (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 then 50% EtOAc/hexanes to give the major diastereomer of 4f (87.5 mg isolated, 56% yield).

HRMS (ESI): m/z calcld for C18H23NO3 [M + H]: 321.1840; found: 321.1860.

1H NMR (500 MHz, CDCl3): 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 calcld for C18H23NO3 [M + H]: 302.1756; found: 302.1743.
$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 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, 2 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**

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610391.

**References**

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(10) For the decomposition of 3k (Scheme 4) via a mechanism reminiscent of serine and threonine dehydratases, see: Grabowski, R.; Hofmeister, A. E. M.; Buckel, W. Trends Biochem. Sci. 1993, 18, 297.


![Scheme 4](image-url)