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Note

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The Conversion of *tert*-Butyl Esters to Acid Chlorides Using Thionyl Chloride

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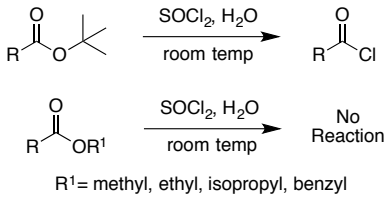
Abstract:



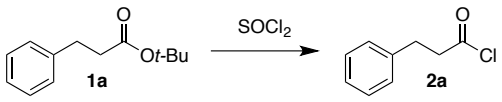
The reaction of *tert*-butyl esters with $SOCl_2$ at room temperature provides acid chlorides in unpurified yields of 89% or greater. Benzyl, methyl, ethyl, and isopropyl esters are essentially unreactive under these conditions, allowing for the selective conversion of *tert*-butyl esters to acid chlorides in the presence of other esters.

Acid chlorides are useful intermediates often used as active esters for the synthesis of carboxylic acid derivatives. They are commonly prepared via the corresponding carboxylic acids which are treated with a chlorinating agent such as $SOCl_2$, PCl_5, $POCl_3$, oxalyl chloride, phosgene, cyanuric chloride, activated triphenylphosphine reagents, and α,α-dichloro ethers, among others.[1] The reaction can be catalyzed by the addition of DMF to generate the Vilsmeier-Haack reagent,[2] which serves as the active chlorinating agent. Other than the widely known conversion of carboxylic acids to acid chlorides there are relatively few instances in the literature of other functional group transformations that can yield acid chlorides directly. Examples include the conversion of lactones,[3] a few *tert*-butyl esters,[4] ethyl chlorofluoroacetate,[5] and tert-

butyldimethylsilyl esters,[6] to the corresponding acid chlorides. In this note, we describe the use of $SOCl_2$ and water or HCl for the conversion of *tert*-butyl esters to acid chlorides in high yields.

This study originated from a need to prepare an acid chloride wherein the corresponding carboxylic acid was difficult to isolate. However, the *tert*-butyl ester was available, and we therefore decided to study the direct conversion of *tert*-butyl esters to acid chlorides. We began with a model substrate, *tert*-butyl dihydrocinnamate (**1a**), and studied a variety of conditions for its conversion dihydrocinnamoyl chloride (**2a**) as described in Table 1. We ran the reaction at room temperature, either in sealed vials or open to the atmosphere, and with or without water or 2,6-di-*tert*-butyl-4-methylpyridine. In the absence of water, the reaction requires 16 h to proceed to high conversion (Table 1, entries 1 and 2). In the presence of water, which presumably reacts with $SOCl_2$ to provide HCl and SO_2, the reaction proceeds to completion in 30 min when sealed (Table 1, entry 4). On larger scale, sealed vessels are less convenient, and as such we studied reactions open to the atmosphere and with water as an additive (Table 1, entries 5-7). These reactions were qualitatively slower, requiring 16 h to proceed to completion. We attribute the decreased rate of reactions in open vessels to the loss of HCl from the mixture, leading to lower concentrations of acid than in sealed vessels from which the HCl cannot escape.[7] This reaction is amenable to scale up and provides similar results on 20 mmol scale when conducted open to the atmosphere in the presence of 1 equiv HCl (a concd aqueous solution was used; 91% yield after purification by distillation; see Table 1, entry 7).

Table 1. Optimization of *tert*-Butyl Ester to Acid Chloride Conditions



1a 2a

Entry	Conditions[a]	Time	Yield[b]

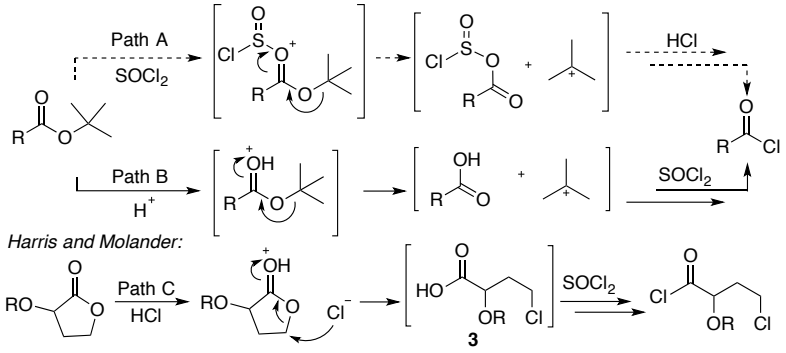
1	Sealed, no additives	0.5 h	9%[c]
2	Sealed, no additives	16 h	83%
3	Sealed, 2,6-di-*tert*-butyl-4-methylpyridine	16 h	0%[c]
4	Sealed, H_2O	0.5 h	91%
5	Open, H_2O	1 h	60%[c]
6	Open, H_2O	16 h	90%
7	Open, HCl, 20 mmol scale	16 h	91%[d]

[a]Sealed reactions were performed in 2 dram (7.4 mL) vials containing a stir bar and capped with a teflon-lined cap. The ester (0.5 mmol, 1 equiv) was dissolved in $SOCl_2$ (5.0 mmol, 10 equiv), treated with additive (1 equiv), then sealed (or left open as indicated) and stirred for the time specified. The vials were then carefully opened, and $SOCl_2$ was removed via azeotropic distillation (2x) with toluene. [b]Yield refers to isolated crude product unless otherwise indicated. [c]Percent conversion was calculated from the ratio of Product:SM by ^{1}H NMR. [d]Yield refers to product isolated after vacuum distillation; 1 equiv of HCl and 20 equiv $SOCl_2$ were used in this experment.

We considered two mechanistic options for this reaction, one in which the ester carbonyl is activated by $SOCl_2$ via complexation followed by loss of *tert*-butyl cation (Scheme 1, path A), the other in which the ester carbonyl is protonated, also resulting in loss of *tert*-butyl cation (Scheme 1, path B).[8] The resulting intermediates would then undergo chlorination with either HCl (path A) or $SOCl_2$ (path B). The addition of 2,6-di-*tert*-butyl-4-methylpyridine can distinguish between these mechanisms. In the presence of this reagent, no reaction is observed

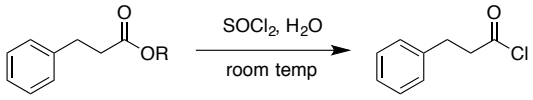
after 16 h (Table 1, entry 3), suggesting that HCl is playing a crucial role in the reaction, consistent with path B. We note that this is mechanistically distinct from the $SOCl_2$-mediated chlorination of lactones, first described by Harris and Molander, which likely proceeds via an S_N2 pathway to provide a chloro-acid, such as **3**, that subsequently undergoes chlorination (Scheme 1, path C).[3]

Scheme 1. Possible Mechanistic Pathways



We then synthesized the methyl, ethyl, isopropyl, and benzyl dihydrocinnamate esters and studied each using the optimized reaction conditions for *tert*-butyl esters (H_2O, sealed vials, 0.5 h), as well as with extended reaction times to 16 h. We observed no conversion to product with all the esters, except benzyl, which provided 1% product after 16 h (Table 2, entry 1-4). These results show that the reaction is highly selective for *tert*-butyl esters under our conditions.

Table 2. Ester Selectivity with Optimized *tert*-Butyl Ester Conditions[a]



entry	R	Conversion at 30 min	Conversion[b] at 16 h
1	Me (**4**)	NR	NR
2	Et (**5**)	NR	NR

3	*i*-Pr (**6**)	NR	NR
4	Bn (**7**)	NR	1%

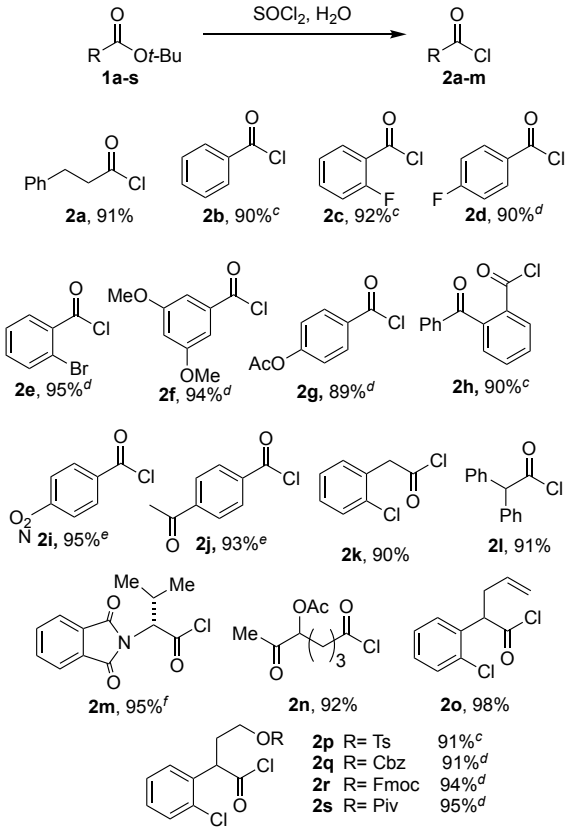
[a]See Table 1 for conditions. [b]Conversion was calculated from the ratio of Product:SM as determined by ^{1}H NMR.

The scope of this method was studied using the substrates shown in Table 3. Acid chlorides can be prepared from electron poor and electron rich aryl *tert*-butyl esters (**2b-j**) as well as from functionalized aliphatic *tert*-butyl esters (**2a, 2k-s)**; however, several substrates required extended reaction times for complete conversion at room temperature (**2b-j, 2p-s**). We found that electron deficient substrates (*p*-acetyl benzoate and *p*-nitro benzoate esters **2i** and **2j**), provided the corresponding carboxylic acid at room temperature, and required heating to 100 °C in toluene to provide acid chloride. We found the reaction conditions are also compatible with terminal olefins, phthalate protected amino acids, and an acetyl functional group (Table 3, **1m-o**).

We wanted to study the stereochemical integrity of stereocenters α-to the carbonyl and prepared compound **1m** derived from D-valine. This compound was subjected to our reaction conditions to provide acid chloride **2m**, which was then converted to the corresponding methyl ester (**3m**; methanol, 10 equiv; Hünigs base, 1.5 equiv; DCM) and observed the product in a 98.4 to 1.6 ratio of enantiomers, indicating that there is minimal erosion of stereochemistry at the α-center in this substrate. We note that the subjection of γ-hydroxy ester **1t** to $SOCl_2$ provides the corresponding lactone (Table 4, entry 1), suggesting that acid chloride formation and lactonization is faster than chlorination of the starting alcohol or the product lactone. Protection of the alcohol **1t** as benzyl or silyl ethers also provided the lactone (Table 4, entry 2-5); however,

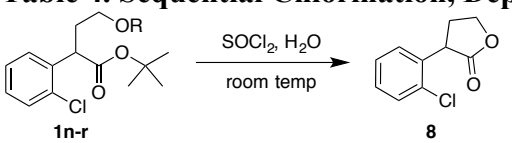
protection as the tosylate, pivalate, or CBZ or Fmoc carbonate provides the desired acid chlorides in good yields (Table 3, **2p-s**).

Table 3. Scope of Chlorination of *tert*-Butyl Esters[a,b]



[a]See Table 1 for conditions. [b]Yields are of isolated products without further purification. [c]Reaction was stirred at 23 °C for 5 h. [d]Reaction was stirred at 23 °C for 16 h. [e]Reaction was performed in toluene (0.1 M) in a sealed 2 dram (7.4 mL) vial at 100 °C for 16 h. [f]Compound **2m** was converted to methyl ester **3m** for HPLC analysis.

Table 4. Sequential Chlorination, Deprotection, and Lactonization[a]

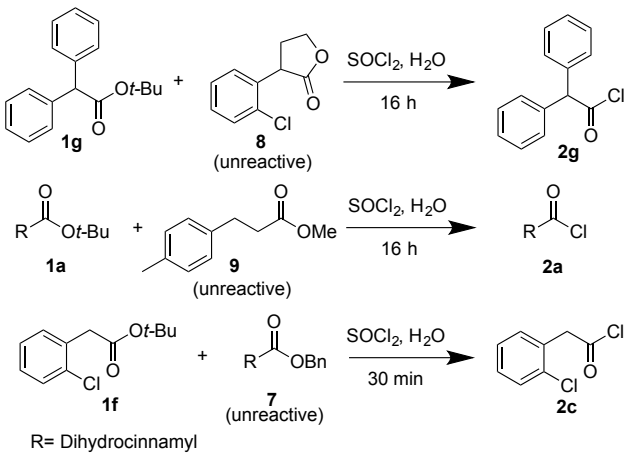


Entry	Compound	R=	Yield[b]
1	**1t**	H	98%
2	**1u**	TES	84%
3	**1v**	TBS	97%
4	**1w**	TIPS	97%
5	**1x**	Bn	94%

[a]See Table 1 for conditions. [b]Yields are of isolated products without further purification.

We wished to confirm the selective conversion of *tert*-butyl esters in the presence of other esters and performed competition experiments between substrates bearing *tert*-butyl esters, and either a lactone, a methyl ester, or a benzyl ester (Scheme 2). In all cases, we obtained complete conversion of the *tert*-butyl ester substrates with no observed acid chloride from the lactone, methyl, or benzyl ester substrates.

Scheme 2. Competition experiments[a,b]



[a]See Table 1 for conditions. [b]Conversion was determined by ^{1}H NMR.

In conclusion, we describe a simple and efficient method for the conversion of *tert*-butyl esters to acid chlorides on a variety of substrates. Our mechanistic studies suggest that the reaction is promoted by acid, and competition experiments show that the reaction is selective for

tert-butyl esters in the presence of methyl, 1°, or 2° esters, and lactones. This method is mild and compatible with other functional groups including alkenes, methyl ethers, protected amines, sulfonates, carbonates, and acetate groups, and provides an alternative to other commonly used methods for acid chloride synthesis.

Experimental Section:

General Information. All reactions were carried out in flame dried glassware under a dry nitrogen atmosphere or sealed in 2 dram (7.4 mL) vials with teflon lined caps as indicated. DCM, diisopropylamine, methanol, ethanol, and isopropanol were distilled from CaH_2 under nitrogen and stored over 3Å molecular sieves prior to use. THF was distilled from Na benzophenone ketyl under nitrogen prior to use. All other reagents were used as received from the supplier. Flash chromatography was performed using 60Å silica gel (40-63 μm). ^{1}H NMR spectra were recorded at 300, 400, or 500 MHz in $CDCl_3$ using residual $CHCl_3$ (7.26 ppm) as an internal reference. ^{13}C NMR spectra were recorded at 75 or 100 MHz in $CDCl_3$ using the center line of the $CDCl_3$ triplet (77.16 ppm) as an internal reference. Infrared (IR) spectra were obtained as thin films on NaCl plates. Exact mass was determined using electrospray ionization (ESI-TOF). We note that in the case of several of the acid chlorides, the corresponding lithiated anhydride is present in the HRMS spectrum and data is provided for the $[M\text{-}Cl]^+$ ion. This ion could be derived from the acid chloride or from the anhydride. In the cases where we report $[M\text{-}Cl]^+$, we were unable to observe the metalated (either lithiated or sodiated) acid chloride, or in some cases to find conditions wherein $[M\text{-}Cl]^+$ is the major ion in the spectrum. We attribute this to the reactive nature of the acid chloride functional group, and the fact that the injection solvent is acetonitrile. This solvent was rigorously dried prior to use, but as it is hygroscopic, it can absorb water as it is

being used in the MS experiment. Compounds **1a**,[9] **1b**,[9] **1i,**[9] **1k**,[10] **4**,[11] **5**,[12] **6**,[13] **7**,[14] **9**,[15] were synthesized according to published procedures.

General procedure for the synthesis of tert-butyl esters:[9] The starting carboxylic acid (5 mmol; 1 equiv) was dissolved in DCM (12.5 ml; 0.25 M) and $MgSO_4$ (20 mmol; 4 equiv) was added. The flask was then purged with N_2 and concd sulfuric acid (4.75 mmol; 0.95 equiv) was added to the suspension followed by *tert*-butanol (25 mmol; 5 equiv). The suspension was allowed to stir overnight at room temperature. The reaction was quenched by the addition of hexanes/EA (1:1; ~50 mL) followed by saturated $NaHCO_3$ (~50 mL; *gas evolution!*). The layers were separated and the organic layer was washed with water (~50 mL; 2x), brine, then dried over $MgSO_4$. The reaction was filtered and concentrated under reduced pressure to provide the crude product as a colorless oil. The crude product was purified by flash chromatography (10:1 hexanes/EA).

tert-Butyl 2-Fluorobenzoate **(1c)** This compound was prepared according to the general procedure to provide **1c** (0.835g, 59%). ^1H and ^{13}C NMR are in accord with those reported in the literature.[16]

tert-Butyl 4-Fluorobenzoate **(1d)** This compound was prepared according to the general procedure to provide **1d** (1.033g, 75%). ^1H and ^{13}C NMR are in accord with those reported in the literature.[16]

tert-Butyl 2-Bromobenzoate (**1e**). This compound was prepared according to the general procedure to provide **1e** (1.452 g, 85%). ^1H and ^{13}C NMR are in accord with those reported in the literature.[17]

tert-Butyl 3,5-Dimethoxybenzoate (**1f**). This compound was prepared according to the general procedure, to provide **1f** (0.579 g, 43%) as a white amorphous powder. R_f = 0.40 (10:1 heanes/EA); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 2.4 Hz, 2H), 6.63 (t, *J* = 2.4 Hz, 1H), 3.84 (s, 6H), 1.60 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 160.5, 133.9, 107.0, 105.0, 81.2, 55.5, 28.1. IR (thin film): C=O, 1713; HRMS (TOF-ESI) m/z calc'd for $C_{13}H_{18}O_4$ $[M+H]^+$, 239.1283; found, 239.1283.

tert-Butyl 4-Acetoxybenzoate (**1g**). Under a nitrogen atmosphere, *tert-butyl 4-hydroxybenzoate* (0.642g, 3.30mmol, 1 equiv. prepared in 1 step following a known procedure)[18] was dissolved in THF-pyridine (1:1, 33 mL) and cooled to 0 °C. Acetyl chloride (0.258 mL, 3.63 mmol, 1.1 equiv) was added dropwise over 15 minutes. A white precipitate forms upon addition. The reaction was allowed to warm to room temperature for 16 h until found to be complete by TLC. Reaction was diluted with hexanes/EA (1:1) and subsequently washed with water (2x), followed by brine, then dried over $MgSO_4$. The reaction was filtered and concentrated to provide **1g** (0.775g, 99% yield) as a yellow oil. R_f = 0.34 (10:1 hexanes/EA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 2H), 2.32 (s, 3H), 1.60 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 165.0, 154.0, 131.0, 129.7, 121.5, 81.2, 28.2, 21.2; IR (thin film): C=O, 1763, 1714 cm^{-1}; HRMS (TOF-ESI) *m/z* calc'd for $C_{13}H_{16}O_4$ $[M+Li]^+$, 243.1209; found, 243.1212.

tert-Butyl 2-Benzoylbenzoate (**1h**). This compound was prepared according to the general procedure to provide **1h** (1.078 g, 86%) as a pale yellow amorphous solid. R_f = 0.34 (10:1 hexanes/EA); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 – 8.00 (m, 1H), 7.82 – 7.77 (m, 2H), 7.60-7.55 (m, 1H), 7.60 – 7.55 (m, 2H), 7.48 – 7.43 (m, 2H), 7.42 – 7.37 (m, 1H), 1.24 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.7, 165.2, 140.9, 137.2, 133.1, 132.0, 131.1, 129.9, 129.6, 129.6, 128.5,

127.6, 82.6, 27.4. IR (thin film): C=O, 1714, 1674 cm^{-1}; HRMS (TOF-ESI) *m/z* calc'd for $C_{18}H_{18}O_3$ $[M+Li]^+$, 289.1416; found, 289.1404.

tert-Butyl 4-Acetylbenzoate (**1j**). This compound was prepared according to the general procedure to provide **1j** (0.645 g, 48%) as a white amorphous powder. ^1H and ^{13}C NMR are in accord with those reported in the literature.[19]

tert-Butyl 2,2-Diphenylacetate (**1l**). This compound was prepared according to the general procedure to provide **1l** (0.588 g, 46%) as a white amorphous solid. ^1H and ^{13}C NMR are in accord with those reported in the literature.[20]

(R)-tert-Butyl 2-(1,2-Dioxoisoindolin-2-yl)-3-methylbutanoate (**1m**). This compound was prepared according to the general procedure to provide **1m** (0.823 g, 64%) as a white amorphous solid. $[\alpha] = 28.2°$ $R_f = 0.32$ (10:1 hexanes/EA); ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, $J = 5.4$, 3.1 Hz, 2H), 7.75 (dd, $J = 5.5$, 3.0 Hz, 2H), 4.51 (d, $J = 8.2$ Hz, 1H), 2.75 (dhept, $J = 8.2$, 6.8 Hz, 1H), 1.43 (s, 9H), 1.15 (d, $J = 6.7$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 167.8, 134.0, 131.7, 123.4, 82.2, 58.6, 28.5, 27.9, 21.0, 19.6; IR (thin film): C=O, 1778, 1720 cm^{-1}; $[\alpha] = 28.2°$; HRMS (TOF-ESI) *m/z* calc'd for $C_{17}H_{21}NO_4$ $[M+Na]^+$, 326.1368; found 326.1370.

tert-Butyl 5-Acetoxy-6-oxoheptanoate (**1n**). 2-Methylcyclohex-2-enyl acetate (0.517 g, 3.35 mmol, 1 equiv, prepared in 4 steps following a known procedure)[21] was dissolved in DCM/*t*BuOH (5:1, 33 mL) and sodium bicarbonate (2.17 g, 25.92 mmol, 4 equiv) was added. The suspension was cooled to -78 °C forming a slurry through which ozone was bubbled for 2 h until starting material was no longer present by TLC. The cold bath was dropped and the reaction was purged with nitrogen. Acetic anhydride (1.84 mL, 19.4 mmol, 3 equiv) and triethylamine

(1.36 mL, 9.72 mmol, 1.5 equiv) were added to the reaction via syringe and and the reaction was stirred overnight at room temperature. The reaction was filtered over celite then washed with 0.1 M HCl, saturated sodium bicarbonate, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a dark red oil. The oil was purified via flash chromatography (4:1 hexanes/EA) to provide **1n** (0.634 g, 38%) as a light yellow oil. R_f = 0.18 (4:1 hexanes/EA); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (dd, *J* = 8.2, 4.2 Hz, 1H), 2.27 (td, *J* = 7.2, 1.7 Hz, 2H), 2.18 (s, 3H), 2.17 (s, 3H), 1.89 – 1.63 (m, 4H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 172.3, 170.5, 80.5, 78.3, 34.8, 29.5, 28.1, 26.1, 20.7, 20.7; IR (thin film): C=O, 1729 cm^{-1}; HRMS (TOF-ESI) *m/z* calc'd for $C_{13}H_{22}LiO_5$ $[M+ H]^+$, 265.1628; found, 265.1625.

tert-Butyl 2-(2-Chlorophenyl)pent-4-enoate **(1o)**. Under a nitrogen atmosphere, diisopropylamine (2.06 mL, 14.68 mmol, 1.05 equiv) was dissolved in THF (140 mL) and cooled to -78 °C. *n*-BuLi (10.23 mL of 1.44 M, 1.1 equiv) was added and the reaction was warmed to 0 °C and stirred for 30 min. The reaction was cooled to -78 °C and compound **1k** (3.17 g, 13.98 mmol in 5 mL) was added via cannula and reaction was stirred at -78 °C for 1 h. The reaction turned bright yellow in color. Allyl bromide (1.27 mL, 14.68 mmol, 1.05 equiv) was added to the reaction dropwise over 10 minutes. The reaction was warmed to room temperature and stirred overnight. The reaction was concentrated under reduced pressure then redissolved in hexanes/EA (5:1), washed with sat. NH_4Cl (2x), brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a deep red oil. The crude material was purified via flash chromatography (50:1 hexanes/EA) to provide **1o** (3.412g, 92%) as a colorless oil. R_f = 0.60 (10:1 hexanes/EA) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.358 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.353 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.22 (td, *J* = 7.5, 1.6 Hz, 1H), 7.16 (td, *J* = 7.6, 1.8 Hz, 1H), 5.80-5.69 (m, 1H), 5.11 – 4.93 (m, 2H), 4.11 (dd, *J* = 8.3, 6.8 Hz, 1H), 2.78 – 2.69 (m, 1H), 2.53-2.43 (m,

1H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 137.0, 135.2, 134.0, 129.6, 128.5, 128.1, 126.9, 116.8, 81.0, 48.1, 36.7, 27.9; IR (thin film): C=O, 1729 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{15}ClH_{19}O_2$ $[M+ Li]^+$, 272.1225; found, 272.1217.

tert-Butyl 2-(2-Chlorophenyl)-4-hydroxybutanoate (**1t**). Compound **1o** (4.81 g, 18.0 mmol) was dissolved in MeOH (180 mL) and cooled to -78 °C. Ozone was bubbled through for 30 minutes until the appearance of a light blue color. Oxygen was bubbled through until the blue color dissipated, then dimethyl sulfide (1.73 mL, 23.4 mmol, 1.3 equiv) was added to the reaction. The reaction was warmed to room temperature and stirred overnight under a nitrogen atmosphere. The reaction was concentrated under reduced pressure to provide a pale yellow residue which was subsequently purified via flash chromatography (10:1 hexanes/EA) to provide the corresponding aldehyde (3.62 g, 75%) as a clear oil. R_f = 0.36 (10:1 hexanes/EA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (X of ABMX; broad s, 1H), 7.40 – 7.36 (m, 1H), 7.26 – 7.17 (m, 3H), 4.55 (M of ABMX, *J* = 9.6, 4.5 Hz, 1H), 3.25 (B of ABMX, *J* = 18.3, 9.6, 1.0 Hz, 1H), 2.74 (A of ABMX, *J* = 18.3, 4.6, 0.7 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.4, 171.2, 136.4, 133.6, 129.9, 128.7, 128.5, 127.2, 81.7, 45.9, 43.1, 27.8; IR thin film: C=O, 1726 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{14}H_{17}ClO_3$ $[M+ Li]^+$, 275.1027; found, 275.1016.

The aldehyde obtained from the above procedure (2.288 g, 8.513 mmol) was dissolved in *tert*-butanol (85 mL) and the flask was purged with nitrogen. Sodium borohydride (0.644 g, 17.02 mmol, 2 equiv) was added to the reaction and was stirred for 15 min until starting material was no longer present by TLC. The reaction was quenched by the addition of water and extracted with ethyl acetate (2x). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a crude colorless oil. The crude residue was purified via flash chromatography (5:1 hexanes/EA) to provide **1t** (2.02 g,

88%) as a clear oil. R_f = 0.23 (5:1 hexanes/EA) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.34 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.24 (td, *J* = 7.4, 1.3 Hz, 1H), 7.21 – 7.16 (m, 1H), 4.22 (X of ABNMX, apparent t, *J* = 7.3 Hz), 3.76-3.55 (M and N of ABMNX, m, 2H), 2.39 – 2.26 (B of ABMNX, m, 1H), 2.01 – 1.91 (A of ABMNX, m, 1H), 1.76 (s, 1H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 137.2, 133.9, 129.7, 128.7, 128.2, 127.0, 81.2, 60.7, 45.6, 35.2, 27.9; IR (thin film): OH, 3449, C=O, 1727cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{14}H_{19}ClO_3$ $[M+ Li]^+$, 277.1183; found, 277.1182.

tert-Butyl 2-(2-Chlorophenyl)-4-(tosyloxy)butanoate (**1p**). Alcohol **1t** (0.315 g, 1.16 mmol) was dissolved in anhydrous pyridine (12 mL) and *p*-toluenesulfonyl chloride (0.443 g, 2.32 mmol, 2 equiv) was added. The flask was purged with nitrogen and stirred at room temperature overnight. The reaction was quenched with the addition of water (100 mL) and subsequently extracted with hexanes/EA (5:1, 2x). The combined organic layers were washed with water (2x), brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a crude colorless oil. The crude material was purified via flash chromatography (10:1 hexanes/EA) to provide **1p** (0.305 g, 62%) as a colorless oil. R_f = 0.20 (10:1 hexanes/EA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.28 (m, 3H), 7.20 – 7.13 (m, 3H), 4.13 – 4.02 (X and N of ABMNX, m, 2H), 3.92 (M of ABMNX, *J* = 9.9, 7.1, 5.6 Hz, 1H), 2.45 – 2.32 (B of ABMNX, m, 4H), 2.10 – 1.96 (A of ABMNX, m, 1H), 1.34 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 144.9, 136.3, 134.1, 133.0, 130.0, 130.0, 128.9, 128.6, 128.0, 127.2, 81.6, 68.2, 45.0, 31.3, 28.0, 21.8; IR (thin film): C=O, 1726 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{21}H_{25}ClO_5S$ $[M+ Li]^+$, 431.1272; found, 431.1268.

tert-Butyl 4-(Benzyloxycarbonyloxy)-2-(2-chlorophenyl)butanoate (**1q**). Under a nitrogen atmosphere, alcohol **1t** (0.224 g, 0.83 mmol, 1 equiv) and DMAP (0.009 g, 0.083 mmol, 0.1

equiv), were dissolved in DCM (8 mL). Triethylamine (0.115 mL, 0.83 mmol, 1 equiv) was then added via syringe, and cooled to 0 °C. Benzylchloroformate (0.236 mL, 1.06 mmol, 2 equiv) was then added to the reaction dropwise via syringe over 15 minutes. The reaction was warmed to room temperature and was stirred for 16 h. The reaction was diluted with hexanes/EA (1:1, 15 mL), washed with water (2x 10 mL), brine, dried over $MgSO_4$, filtered and concentrated to provide a crude colorless oil. The crude residue was purified via flash chromatography (20:1 hexanes/EA) to provide **1q** (0.080g, 24%) as a colorless oil. R_f = 0.20 (20:1 hexanes/EA); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.32 (m, 6H), 7.30 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.22 (td, *J* = 7.5, 1.7 Hz, 1H), 7.19 (td, *J* = 7.5, 1.9 Hz, 1H), 5.15 (s, 2H), 4.22 – 4.09 (M, N, and X of ABMNX, m, 3H), 2.44 (B of ABMNX, *J* = 13.6, 7.3, 6.1 Hz, 1H), 2.09 (A of ABMNX, *J* = 13.7, 7.4, 6.2 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 155.1, 136.7, 135.3, 134.1, 129.9, 128.7, 128.7, 128.6, 128.5, 128.4, 127.2, 81.4, 77.2, 69.7, 65.9, 45.2, 31.4, 28.0; IR (thin film): C=O, 1747, 1728 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{22}H_{25}ClO_5$ $[M+Li]^+$, 410.1542; found, 410.1535.

tert-Butyl 4 (((9H-fluoren-9-yl) methoxy)carbonyloxy)-2-(2-chlorophenyl)butanoate (**1r**). Under a nitrogen atmosphere, alcohol **1t** (0.272 g, 1.00 mmol) dissolved in pyridine (5 mL) was added dropwise via cannula to 9-fluorenylmethoxycarbonyl (Fmoc) chloride (0.312 g, 1.20 mmol, 1.2 equiv) dissolved in pyridine (5 mL). The reaction was stirred at room temperature overnight. Water (15 mL) was added to quench the reaction and was subsequently extracted with EA (2x). The combined organic layers were washed with brine (2x), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a brown oil. The crude residue was purified via flash chromatography (20:1 hexanes/EA) to provide **1r** (0.180 g, 37%) as a colorless oil. R_f = 0.20 (10:1 hexanes/EA); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 2H), 7.63 (d, *J* = 7.5

Hz, 2H), 7.46 – 7.36 (m, 3H), 7.37 – 7.30 (m, 3H), 7.26 – 7.14 (m, 2H), 4.39 (d, *J* = 7.8 Hz, 2H), 4.30 – 4.17 (X and N of ABMNX, m, 2H), 4.13 (M of ABMNX, *J* = 10.8, 7.2, 6.0 Hz, 1H), 2.48 (B of ABMNX, *J* = 13.6, 7.3, 6.1 Hz, 1H), 2.13 (A of ABMNX, *J* = 13.8, 7.5, 6.2 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 155.2, 143.5, 143.5, 141.4, 136.8, 134.2, 130.0, 128.7, 128.6, 128.0, 127.3, 127.3, 125.3, 125.3, 120.2, 81.5, 69.9, 66.0, 46.9, 45.2, 31.5, 28.0; IR (thin film): C=O, 1747, 1728 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{29}H_{29}ClO_5$ $[M+Li]^+$, 499.1864; found, 499.1862.

tert-Butyl 2-(2-Chlorophenyl)-4-(pivaloyloxy)butanoate (**1s**). Under a nitrogen atmosphere, alcohol **1t** (0.265 g, 0.979 mmol, 1 equiv) and DMAP (0.002 g, 0.019 mmol, 0.2equiv) were dissolved in DCM (10 mL). Triethylamine (0.177 mL, 1.27 mmol, 1.3 equiv) was added via syringe, and the reaction was cooled to 0 °C. Trimethylacetyl chloride (0.145 mL, 0.117 mmol, 1.2 equiv) was added dropwise via syringe to the reaction over 10 minutes. The reaction was warmed to room temperature and stirred for 16 h. The reaction was diluted with hexanes/EA (1:1, 15 mL), washed with water (2x), brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a yellow oil. The crude material was purified via flash chromatography (20:1 hexanes/EA) to provide **1m** (0.262 g, 76%) as a colorless oil. R_f = 0.52 (10:1 hexanes/EA); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.33 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.24 (td, *J* = 7.5, 1.5 Hz, 1H), 7.19 (td, *J* = 7.6, 1.8 Hz, 1H), 4.20 (X of ABMNX apparent t, *J* = 7.5 Hz, 1H), 4.08 (N of ABMNX, *J* = 11.1, 7.3, 5.7 Hz, 1H), 3.99 (M of ABMNX, *J* = 11.1, 6.2 Hz, 1H), 2.40 – 2.30 (B of ABMNX, m, 1H), 2.07 (A of ABMNX, *J* = 14.3, 7.3, 5.9 Hz, 1H), 1.40 (s, 9H), 1.20 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 172.1, 136.9, 134.2, 129.9, 128.7, 128.5, 127.3, 81.4, 62.2, 45.2, 38.9, 31.6, 28.0, 27.3; IR (thin film):

C=O, 1729 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{19}H_{27}ClO_4$ $[M+Li]^+$, 360.1749; found, 360.1747.

tert-Butyl 2-(2-Chlorophenyl)-4-triethylsilyloxy)butanoate (**1u**). Alcohol **1t** (0.197 g, 0.727 mmol) was dissolved in DCM (7 mL) and cooled to 0 °C under a nitrogen atmosphere. Triethylamine (0.202 mL, 1.45 mmol, 2 equiv) then triethylsilyl trifluoromethanesulfonate (TESOTf) (0.164 mL, 0.272 mmol, 1 equiv) were added to the reaction dropwise via syringe. The reaction was stirred at 0 °C for 1 h until starting material could no longer be observed by TLC. The reaction was diluted with hexanes/EA (1:1), washed with $NaHCO_3$ (sat.), water, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a light pink oil. The crude residue was purified via flash chromatography (10:1 hexanes/EA) to provide **1u** (0.197 g, 70%) as a colorless oil. R_f = 0.48 (10:1 hexanes/EA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.33 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.22 (td, *J* = 7.5, 1.6 Hz, 1H), 7.17 (td, *J* = 7.5, 1.9 Hz, 1H), 4.22 (X of ABMNX, *J* = 8.0, 6.8 Hz, 1H), 3.68 – 3.52 (M and N, of ABMNX, m, 2H), 2.29 (B of ABMNX, *J* = 12.8, 8.0, 6.3 Hz, 1H), 1.94 (A of ABMNX, *J* = 13.4, 6.6 Hz, 1H), 1.39 (s, 9H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.57 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 137.9, 134.5, 130.1, 129.2, 128.4, 127.3, 81.3, 60.9, 45.4, 35.8, 28.4, 7.2, 4.8; IR (thin film): C=O,1729 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{20}H_{33}ClO_3Si$ $[M+Li]^+$, 391.2048; found, 391.2047.

tert-Butyl 4-(tert-Butyldimethylsilyloxy)-2-(2-chlorophenyl)butanoate (**1v**). Alcohol **1t** (0.478 g, 1.76 mmol) was dissolved in THF (18 mL), imidazole (0.359 g, 5.28 mmol, 3 equiv) was added, and the flask was purged with nitrogen. *tert*-Butyldimethylsilylchloride (TBDMSCl) (0.346 g, 2.3 mmol, 1.3 equiv, in 2 mL of THF) was then added via cannula and the reaction was stirred at room temperature. After a few seconds a white precipitate formed in the reaction. After 30

minutes the reaction was found to be complete by TLC. The reaction was diluted with hexanes/EA (1:1) washed with water (2x), brine, dried over $MgSO_4$, filtered, and concentrated to provide a colorless oil. The crude product was purified via flash chromatography to provide **1v** (0.450 g, 66%) as a colorless oil. R_f = 0.31 (10:1 hexanes/EA); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.35 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.23 (td, *J* = 7.5, 1.5 Hz, 1H), 7.19 (td, *J* = 7.6, 1.8 Hz, 1H), 4.26 (X of ABMNX, *J* = 8.1, 6.7 Hz, 1H), 3.66 – 3.55 (M and N of ABMNX, m, 2H), 2.27 (B of ABMNX, *J* = 14.0, 8.0, 6.0 Hz, 1H), 1.94 (A of ABMNX, *J* = 13.4, 6.6 Hz, 1H), 1.41 (s, 9H), 0.90 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 137.5, 134.0, 129.6, 128.8, 127.9, 126.8, 80.8, 60.6, 44.8, 35.3, 27.9, 25.9, 18.2, -5.4, -5.5; IR (thin film): C=O, 1729 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{20}H_{33}ClO_3Si$ $[M+ Li]^+$, 391.2048; found 391.2043.

tert-Butyl 2-(2-Chlorophenyl)-4-(triisopropylsilyloxy)butanoate (**1w**). Alcohol **1t** (0.336 g, 1.24mmol) was dissolved in THF (12 mL) at room temperature, imidazole (0.253 g, 3.72 mmol, 3 equiv) was added, and the flask was purged with nitrogen. Triisopropylsilyl chloride (TIPSCl) (0.345 mL, 1.61 mmol, 1.3 equiv) was added to the solution dropwise via syringe. A white precipitate was observed and the reaction was stirred overnight at room temperature until starting material was no longer present by TLC. The reaction was diluted with hexanes/EA (1:1) and subsequently washed with water (2x), brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a colorless oil. The crude product was purified via flash chromatography (20:1 hexanes/EA) to provide **1w** (0.280g, 53%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 6.2, 1.3 Hz, 1H), 7.34 (dd, *J* = 6.4, 1.2 Hz, 1H), 7.22 (td, *J* = 7.5, 1.5 Hz, 1H), 7.16 (td, *J* = 7.6, 1.8 Hz, 1H), 4.31 (X of ABMNX, *J* = 8.3, 6.4 Hz, 1H), 3.69 (M and N of ABMNX, *m,* Hz, 2H), 2.27 (B of ABMNX, *J* = 14.0, 8.3, 5.8 Hz, 1H), 1.94 (A of

ABMNX, J = 13.4, 6.6 Hz, 1H), 1.39 (s, 9H), 1.12 – 0.97 (m, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 137.6, 134.0, 129.6, 128.8, 127.9, 126.8, 80.7, 60.9, 44.8, 35.5, 27.9, 18.0, 11.9; IR (thin film): C=O, 1729 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{23}H_{39}ClO_3Si$ $[M+ Li]^+$, 433.2517; found 433.2517.

tert-Butyl 4-(Benzyloxy)-2-(2-chlorophenyl)butanoate (**1x**). Under a nitrogen atmosphere, alcohol **1t** (0.286 g, 1.06 mmol, 1 equiv) was dissolved in 1,4-dioxane (10 mL). Benzyl 2,2,2-trichloroacetimidate (0.392 mL, 0.212 mmol, 2 equiv) and triflic acid (0.019 mL, 0.212 mmol, 0.2 equiv) were added to the reaction via syringe and stirred at room temperature for 16 h. Reaction was diluted with hexanes/EA (1:1), and the organic layer was washed with $NaHCO_3$ sat. (2x), brine, dried over $MgSO_4$, filtered, and concentrated to provide a tan solid. The crude product was purified via flash chromatography (50:1 hexanes/EA) to provide **1x** (0.118 g, 31%) as a colorless oil. R_f = 0.21 (50:1 hexanes/EA); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, J = 7.8, 1.6 Hz, 1H), 7.35 – 7.31 (m, 5H), 7.29-7.27 (m, 1H), 7.22 (td, J = 7.5, 1.6 Hz, 1H), 7.18 (td, J = 7.6, 1.9 Hz, 1H), 4.48 (B of AB, J = 11.9 Hz, 1H), 4.45 (A of AB, J = 11.9 Hz, 1H), 4.26 (X of ABMNX, apparent t, J = 7.4 Hz, 1H), 3.50 (N of ABMNX, J = 9.5, 6.0 Hz, 1H), 3.39 (M of ABMNX, J = 9.5, 7.3, 5.8 Hz, 1H), 2.40 (B of ABMNX, J = 13.5, 7.4, 6.0 Hz, 1H), 2.04 (A of ABMNX, J = 13.6, 7.5, 5.9 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 138.5, 137.4, 134.2, 129.8, 129.0, 128.5, 128.2, 127.8, 127.7, 127.1, 81.0, 73.1, 67.9, 45.6, 32.5, 28.0; IR (thin film): C=O, 1726 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{21}H_{25}ClO_3$ $[M+Li]^+$, 367.1653; found, 367.1654.

General Procedure for the synthesis of acid chlorides: The *tert*-butyl ester (1 mmol; 1 equiv) was dissolved in $SOCl_2$ (0.70 mL; 10 mmol; 10 equiv) in a 2 dram (7.4 mL) vial equipped with a magnetic stir bar at room temperature. Water (18 μl; 1mmol; 1 equiv) was then added and the

vial was capped with a teflon-lined cap. *Note that the vial was never filled more than 40% full to avoid the possibility of rupture!* The reaction was stirred, at which point, gas evolution was observed. Stirring was continued for the length of time indicated in Table 5. The cap was then carefully removed (*Caution: contents under pressure!*), and toluene (1 mL) was added to the vial and removed at reduced pressure to effect azeotropic removal of $SOCl_2$ and provide the product.

Large scale acid chloride synthesis open to atmosphere: *3-Phenylpropanoyl Chloride* **(2a)** The *tert*-butyl dihydrocinnamate (4.174 g, 20.2 mmol, 1 equiv) was dissolved in $SOCl_2$ (20 equiv, 28.5 mL) equipped with a magnetic stir bar at room temperature. Concd HCl (1 equiv, 1.66 mL) was then added and the flask was subsequently capped with a polyethylene cap that was punctured with a 21g needle for a vent to the atmosphere. The reaction was stirred, at which point, gas evolution was observed, and stirring continued for 16 h at room temperature. Toluene (5 ml x2) was added to the flask and removed at reduced pressure to effect azeotropic removal of $SOCl_2$. The crude material was isolated in a 98% yield. The crude material was then subjected to vacuum distillation to isolate product as a clear oil (3.102g, 91% yield).

3-Phenylpropanoyl Chloride (**2a**). This compound was prepared according to the general procedure to provide **2a** (0.101 g, 91%) as a colorless oil. ^{1}H and ^{13}C NMR are in accord with those reported in the literature.[22]

Benzoyl Chloride (**2b**). This compound was prepared according to the general procedure with an extended reaction time of 5 h to provide **2b** as a colorless oil (0.110 g, 90%). ^{1}H and ^{13}C NMR are in accord with those reported in the literature.[23]

2-Fluorobenzoyl Chloride (**2c**) This compound was prepared according to the general procedure with an extended reaction time of 5 h to provide **2c** as a pale yellow oil (0.046 g, 92%). ^{1}H and ^{13}C NMR are in accord with those reported in the literature.[24]

4-Fluorobenzoyl Chloride (**2d**) This compound was prepared according to general procedure with an extended reaction time of 16 h to provide **2d** as a pale yellow oil (0.062 g, 90%). ^{1}H and ^{13}C NMR are in accord with those reported in the literature.[25]

2-Bromobenzoyl Chloride (**2e**). This compound was prepared according to the general procedure to provide **2e** (0.044 g, 95%) as a colorless oil.[26]

3,5-Dimethoxybenzoyl Chloride (**2f**). This compound was prepared according to the general procedure with extended reaction time to 16 h to provide **2f** (0.080 g, 94%). ^{1}H and ^{13}C NMR are in accord with those reported in the literature.[27]

4-(Chlorocarbonyl)phenyl Acetate (**2g**). This compound was prepared according to the general procedure with extended reaction time to 16 h to provide **2g** (0.054, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 167.5, 156.2, 133.2, 130.7, 122.4, 21.3. IR (thin film): C=O, 1774 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_9H_7O_3$ $[M\text{-}Cl]^+$, 163.0395; found, 163.0413.

2-Benzoylbenzoyl Chloride (**2h**) This compound was prepared according to the general procedure with extended reaction time to 16 h to provide **2h** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.6 Hz, 1H), 7.79 (apparent t, J = 7.5 Hz, 1H), 7.74 – 7.68 (m, 3H), 7.64 (apparent t, J = 7.4 Hz, 1H), 7.46 – 7.41 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 151.3, 138.2, 135.5, 130.9, 130.0, 128.8, 126.0, 125.9, 123.6, 123.5, 110.1, 99.9. IR (thin film): C=O, 1791 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{14}H_9O_2Cl$ $[M+Li]^+$, 251.0451; found, 251.0442.

4-Nitrobenzoyl Chloride (**2i**) This compound was prepared according to the general procedure with extended reaction time to 16 h and run in toluene (0.1 M), heated to 100 °C to provide **2i** (0.080 g, 94%) ^{1}H and ^{13}C NMR are in accord with those reported in the literature.[28]

4-Acetylbenzoyl Chloride (**2j**) This compound was prepared according to the general procedure with extended reaction time to 16 h and run in toluene (0.1 M) heated to 100 °C to provide **2j** (0.054 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.21 (m, 2H), 8.10 – 8.06 (m, 2H), 2.69 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.1, 168.0, 141.8, 136.6, 131.7, 128.7, 27.2; IR (thin film): C=O, 1773, 1736, 1687 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_9H_7O_2$ $[M\text{-}Cl]^+$, 147.0446; found, 147.0451.

2-(2-Chlorophenyl)acetyl Chloride. (**2k**). This compound was prepared according to the general procedure to provide **2k** (0.072 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 1H), 7.32 – 7.23 (m, 3H), 4.28 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 134.7, 131.6, 130.2, 129.9, 129.8, 127.2, 50.8; IR (thin film): C=O, 1798 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for C_8H_6OCl $[M\text{-}Cl]^+$, 153.0107; found 153.0104 (minor component).

2,2-Diphenylacetyl Chloride (**2l**). This compound was prepared according to the general procedure to provide **2l** as an off-white amorphous solid (0.064 g, 91%). ^{1}H and ^{13}C NMR are in accord with those reported in the literature.[29]

(R)-2-(1,3-Dioxoisoindolin-2-yl)-3-methylbutanoyl Chloride (**2m**). This compound was prepared according to the general procedure to provide **2m** as a white solid (0.070 g, 95%). Mp = 117-119 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, J = 5.5, 3.1 Hz, 2H), 7.82 (dd, J = 5.5, 3.0 Hz, 2H), 4.76 (d, J = 8.4 Hz, 1H), 2.77 (dhept, J = 8.5, 6.8 Hz, 1H), 1.18 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 167.1, 134.8, 131.5, 124.1, 77.2, 66.5, 29.3,

20.5, 19.2. IR (thin film): C=O, 1805, 1784, 1723 cm^{-1}; [α] = 101.6°; HRMS (TOF-ESI) *m/z* calc'd for $C_9ClH_{13}NO_4$ $[M-Cl]^+$, 230.0817; found, 230.0811.

(R)-methyl 2-(1,3-dioxoisoindolin-2-yl)-3-methylbutanoate (**3m**). Compound **2m** (0.026 g, 0.098 mmol,1 equiv) dissolved in DCM (0.5 mL), was added via cannula to a solution of MeOH (.040 mL, 0.98mmol, 10 equiv), Hunigs base (0.025 mL, 1.5 equiv) in DCM (0.1 M). The reaction was left to stir for 1h until there was no change by TLC. Reaction was diluted with 1:1 hexanes:EtOAc then subsequently washed with sat. sodium bicarbonate (2x), brine, dried of over $MgSO_4$, filtered, and concentrated to obtain crude material as a colorless oil. The crude product was purified via flash chromatography (10:1 hexanes/EA) to provide **3m** as a colorless oil (0.022g, 85% yield). ^1H and ^{13}C NMR are in accord with those reported in the literature.[30]

7-Chloro-2,7-dioxoheptan-3-yl Acetate **(2n)**. This compound was prepared according to the general procedure to provide **2n** (0.093 g, 95%) as a brown oil. ^1H NMR (500 MHz, $CDCl_3$) δ 5.02 (m, *J* = 7.5, 4.0 Hz, 1H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.19 (s, 3H), 2.18 (s, 3H), 1.93 – 1.76 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6, 173.3, 170.4, 77.7, 46.3, 28.6, 26.1, 20.7, 20.6; IR (thin film): C=O, 1799, 1759, 1729 cm^{-1}; HRMS (TOF-ESI) *m/z* calc'd for $C_9ClH_{13}O_4$ $[M+ Li]^+$, 227.0663; found, 227.0663.

2-(2-Chlorophenyl)pent-4-enoyl Chloride **(2o).** This compound was prepared according to the general procedure to provide **2o** (0.082 g, 98%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 1H), 7.32 – 7.22 (m, 3H), 5.70 (ddt, *J* = 17.0, 10.2, 6.9 Hz, 1H), 5.12 – 5.03 (m, 2H), 4.66 (apparent t, *J* = 7.4 Hz, 1H), 2.92 – 2.84 (m, 1H), 2.62 – 2.53 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 134.4, 133.7, 133.1, 130.1, 129.5, 129.0, 127.4, 118.5, 59.0, 36.6; IR (thin film): C=O 1793 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{11}Cl_2H_{10}O$ $[M+ Li]^+$, 234.0260; found, 234.0265.

4-Chloro-3-(2-chlorophenyl)-4-oxobutyl 4-Methylbenzenesulfonate (**2p**). This compound was prepared according to the general procedure with extended reaction time to 5 h to provide **2p** (0.042 g, 91%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 2H), 7.42 – 7.37 (m, 1H), 7.32 (d, J = 8.1 Hz, 2H), 7.30-7.22 (m, 2H), 7.16 – 7.11 (m, 1H), 4.60 (X of ABMNX, J = 7.8, 6.7 Hz, 1H), 4.06 (N of ABMNX, J = 10.3, 6.4, 5.0 Hz, 1H), 3.88 (M of ABMNX, J = 10.3, 7.7, 4.7 Hz, 1H), 2.51 (B of ABMNX, J = 14.7, 7.8, 6.8, 5.0 Hz, 1H), 2.43 (s, 3H), 2.15 (A of ABMNX, J = 14.5, 7.9, 6.4, 4.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 145.2, 134.4, 133.1, 132.6, 130.6, 130.1, 130.0, 129.7, 128.0, 127.8, 66.8, 55.8, 31.4, 21.8; IR (thin film): C=O, 1796 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{17}H_{16}Cl_2O_4S$ $[M+ Li]^+$, 393.0307; found, 393.0323.

Benzyl 4-Chloro-3-(2-chlorophenyl)-4-oxobutylcarbonate (**2q**). This compound was prepared according to the general procedure with extended reaction time to 16 h to provide **2q** (0.009 g 91%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (dt, J = 6.0, 3.4 Hz, 1H), 7.40 – 7.33 (m, 5H), 7.32 – 7.27 (m, 2H), 7.25 – 7.21 (m, 1H), 5.16 (s, 2H), 4.72 (X of ABMNX, J = 8.2, 6.4 Hz, 1H), 4.17 (N of ABMNX, J = 11.4, 5.7 Hz, 1H), 4.02 (M of ABMNX, J = 11.1, 8.0, 5.1 Hz, 1H), 2.57 (B of ABMNX, J = 14.5, 7.9, 6.5, 5.5 Hz, 1H), 2.19 (A of ABMNX, J = 14.4, 8.2, 6.0, 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 154.9, 135.2, 134.6, 133.5, 130.6, 130.0, 129.4, 128.8, 128.5, 127.9, 77.2, 69.9, 64.7, 56.1, 31.5; IR (thin film): C=O, 1794, 1747 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{18}H_{16}Cl_2O_4$ $[M+Li]^+$, 372.0577; found, 372.0576.

(9H-fluoren-9-yl)methyl 4-Chloro-3-(2-chlorophenyl)-4-oxobutanylcarbonate (**2r**). This compound was prepared according to the general procedure to provide **2r** (0.016 g, 94%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dt, J = 7.5, 0.9 Hz, 2H), 7.62 (ddd, J = 7.5, 2.2, 1.0 Hz, 2H), 7.49 – 7.45 (m, 1H), 7.43 – 7.40 (m, 2H), 7.37 – 7.29 (m, 4H), 7.27 – 7.23 (m, 1H),

4.77 (X of ABMNX, J = 8.2, 6.5 Hz, 1H), 4.42 (B of AB, J = 1.6 Hz, 1H), 4.40 (A of AB, J = 1.0 Hz, 1H), 4.20 (N of ABMNX, J = 11.3, 5.7 Hz, 1H), 4.05 (M of ABMNX, J = 11.1, 8.0, 5.1 Hz, 1H), 2.61 (B of ABMNX, J = 14.6, 8.1, 6.5, 5.4 Hz, 1H), 2.22 (A of ABMNX, J = 14.4, 8.2, 6.0, 5.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 155.0, 143.4, 143.4, 141.4, 134.7, 133.5, 130.6, 130.0, 129.3, 128.1, 127.9, 127.3, 127.3, 125.3, 125.3, 120.2, 70.1, 64.8, 56.1, 46.9, 31.5; IR (thin film): C=O, 1791 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{25}H_{20}Cl_2O_4$ $[M+Li]^+$, 461.0899; found, 461.0902.

4-Chloro-3-(2-chlorophenyl)-4-oxobutyl pivalate **(2s)**. This compound was prepared according to the general procedure to provide **2s** (0.036 g, 95%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.44 (m, 1H), 7.35 – 7.27 (m, 3H), 4.76 (X of ABMNX, J = 7.1 Hz, 1H), 4.14 (bs, 1H), 4.00 (bs, 1H), 2.54 (bs, 1H), 2.17 (bs, 1H), 1.23 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 174.1, 134.5, 133.6, 130.5, 129.9, 129.1, 127.8, 61.4, 56.3, 38.9, 31.8, 27.3; IR (thin film): C=O 1793, 1729 cm^{-1}. HRMS (ESI-TOF) *m/z* calc'd for $C_{15}H_{18}ClO_3$ $[M-Cl]^+$, 281.0945; found, 281.0934.

3-(2-Chlorophenyl)dihydrofuran-2(3H)-one (**8**). This compound was prepared according to the general procedure with extended reaction time to 16 h to provide **8** as a colorless oil, (84-98%), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dt, J = 7.3, 1.2 Hz, 1H), 7.35 – 7.22 (m, 3H), 4.52 (N of ABMNX, J = 8.8, 2.9 Hz, 1H), 4.40 (M of ABMNX, J = 9.4, 6.7 Hz, 1H), 4.25 (X of ABMNX, J = 10.7, 9.2 Hz, 1H), 2.87 – 2.73 (B of ABMNX, m, 1H), 2.38 (A of ABMNX, J = 12.8, 10.7, 9.7, 8.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 135.0, 134.2, 130.1, 129.6, 129.2, 127.6, 66.7, 44.0, 31.0; IR (thin film): C=O, 1771 cm^{-1}; HRMS (ESI-TOF) *m/z* calc'd for $C_{10}H_9ClO_2$ $[M+Li]^+$, 203.0451; found, 203.0453.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of products for the reactions described in Tables 3 and 4 are provided. The material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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