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Electrophilic Etherification of α-Heteroaryl Carbanions with Monoperoxyacetals as a Route to Ketene *O,O*- and *N,O*-Acetals

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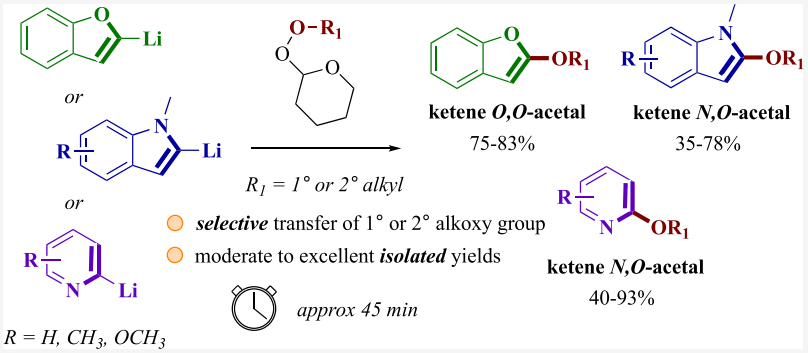
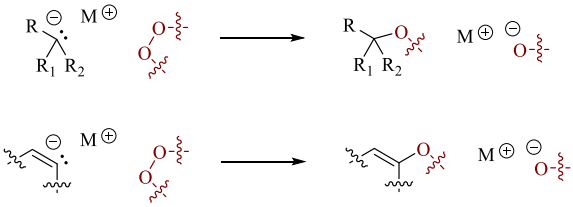


ABSTRACT: Alkyl ketene acetals are useful reactants in a variety of synthetic processes, and yet, there are limited routes to their formation as isolable products. We now report the successful synthesis and isolation of heteroaryl ketene acetals through intermolecular transfer of alkoxyl (δ^+OR) from electrophilic peroxides to lithiated benzofurans, indoles, and pyridines. Primary and secondary peroxyacetals enable selective transfer of the nonanomeric alkoxy group in moderate to high yield; substrates bearing an electron-donating substituent show enhanced reactivity toward electrophilic oxygen. Heteroaryl ketene acetals are remarkably stable throughout traditional purification techniques; the superior stability of ketene *N,O*-acetals compared to ketene *O,O*-acetals is presumably due to increased aromaticity of the indole and pyridine structures. The presented method overcomes typical problems associated with alkyl ketene acetal synthesis as reported products withstood workup and flash column chromatography procedures.

INTRODUCTION

Ketene acetals are an important class of organic reactants and intermediates.[1] Specifically, ketene *O,O*- or *N,O*-acetals have proven useful as synthons in α, β-unsaturated ester production,[2] lactone synthesis,[3] uncatalyzed polymerization,[4] nontraditional aldol condensation,[5] anodic olefin coupling,[6] Claisen rearrangements,[7] and Diels−Alder reactions.[8] Although ketene acetals are widely used in many synthetic processes, methods of their synthesis are dominated by silylation of ester enolates (Figure 1, A).[2−5,9] Moreover, reports of isolable, silyl ketene acetals do exist and are easily accessible.[2−7,9b,c] However, the synthesis of alkyl ketene *O,O*- or *N,O*-acetals is more challenging. The tendency for alkyl ketene acetals to undergo hydration or acid-catalyzed, nucleophilic addition makes this functional group elusive and difficult to isolate.[1b,10]

Due to these limitations, previous synthesis of alkyl ketene acetals has been primarily limited to dehydrohalogenation of alkyl halides,[11] pyrolysis of orthoesters,[12] or conjugate addition−elimination reactions (Figure 1, B−D).[13] Nonetheless, non-silyl ketene acetals are generally used *in situ*, providing few reports of their isolation.[14] Our lab became interested in a potential method of synthesizing stable ketene *O,O*- and *N,O*-acetals based upon C−O bond formation. Due to the electron-rich nature of ketene acetals, an oxygen-centered electrophile appeared to be the most appropriate method for alkoxy transfer (δ^+OR). Therefore, we turned our attention to the use of carbon nucleophiles and electrophilic peroxides for intermolecular etherification, as demonstrated by several groups throughout the last century (eqs 1 and 2).[15−21]



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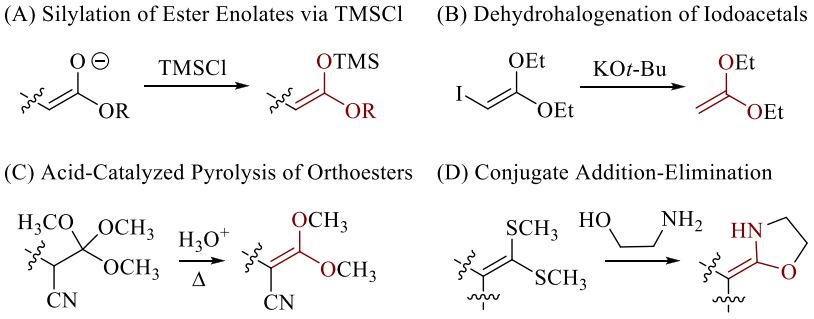


Figure 1. Select, previous methods of producing (A) silyl ketene acetals using trimethylsilyl chloride (TMSCl), (B,C) simple, ketene *O,O*-acetals, or (D) ketene *N,O*-acetals.

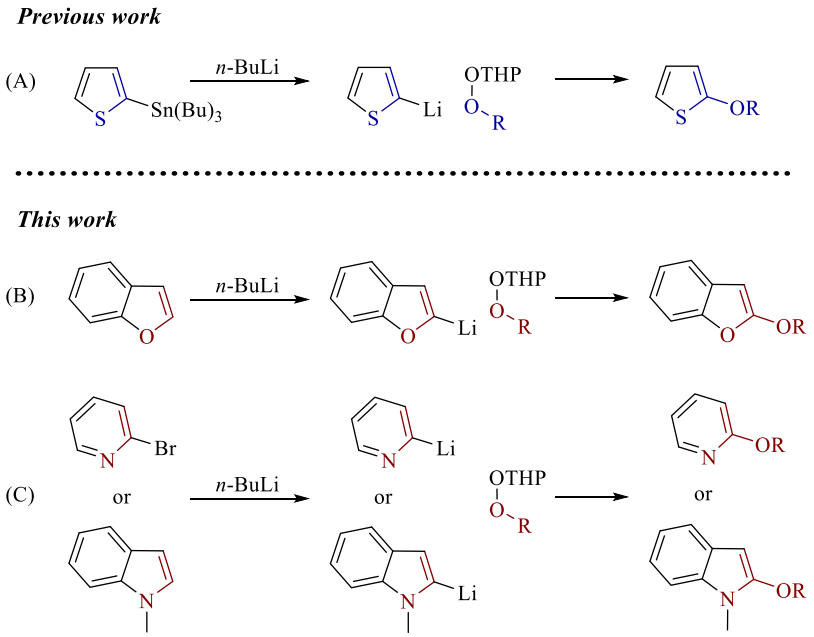


Figure 2. (A) Previous use of metalated thiophenes for intermolecular C−O bond formation. (B) Ketene *O,O*-acetal synthesis reported herein. (C) Application of intermolecular etherification between α-heteroaryl carbanions and electrophilic peroxides to the formation of ketene *N,O*-acetals.

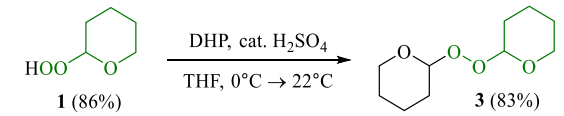
Furthermore, we were encouraged by reports of successful alkoxy transfer to sp^2-hybridized organometallics[17,22] and were optimistic that the same chemistry could be applied to the production of stable, heteroaryl ketene acetals.

Although the use of carbanion/peroxide chemistry has been applied to the synthesis of oxacycles,[18] difluoro ethers,[19] anticancer analogues,[20] and 2-deoxyglycosides,[21] etherification using nucleophiles derived from aromatic heterocycles is limited to the cursory use of thiophenes (Figure 2, A).[17]

We now demonstrate the production of isolable, aromatic ketene *O,O*-acetals using sp^2-hybridized, ether carbanions and a series of monoperoxyacetals (Figure 2, B). Additionally, we introduce the application of intermolecular etherification utilizing carbanions/peroxides to the production of isolable ketene *N,O*-acetals derived from a set of biologically relevant, aromatic heterocycles (Figure 2, C).

RESULTS

Primary, secondary, unsaturated, and bis-monoperoxyacetal electrophiles were produced via acid-catalyzed acetalization of dihydropyran (DHP) with tetrahydropyranyl (THP) hydroperoxide (**1**) (**3**, eq 3),[17,23] Ag_2O-mediated alkylation of an allylic bromide (**4**) with hydroperoxides (**5**, eq 4),[17,24] or



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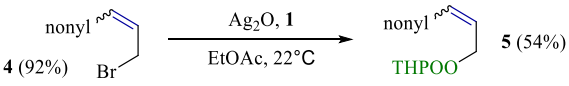

(4)

peroxidation of trifluoromethanesulfonates ("triflate" substrates, **6**−**11**, were previously prepared from their corresponding alcohol; monoperoxyacetals: **12**, **13a**, **14a**, **15**−**17**, Table 1).

Additionally, dialkyl peroxides were prepared through the coupling of *tert*-butyl hydroperoxide (**2**) and trifluoromethanesulfonates (**13b**, **14b**; Table 1).[17,19,25] Consistent with previous reports, primary peroxide substrates were isolated in good to excellent yields.[26] The synthesis of a branched electrophile (**17**) via S_N2 displacement at a secondary carbon proceeded with impressive success despite the difficulties typically associated with this type of transformation.[27]

Synthesis and Reactivity of Ketene *O,O*-Acetals. Scheme 1 illustrates initial efforts of ketene acetal formation

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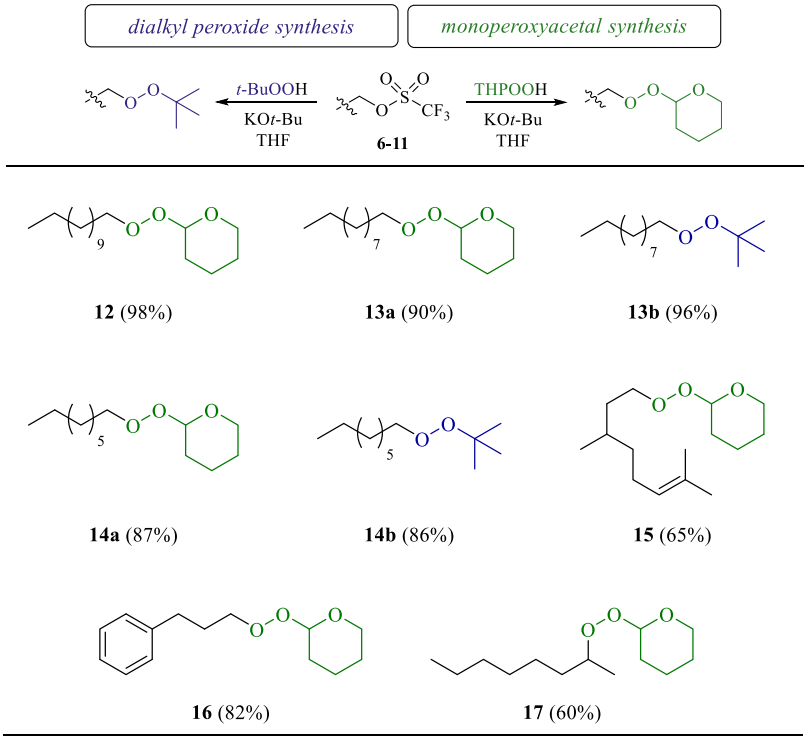
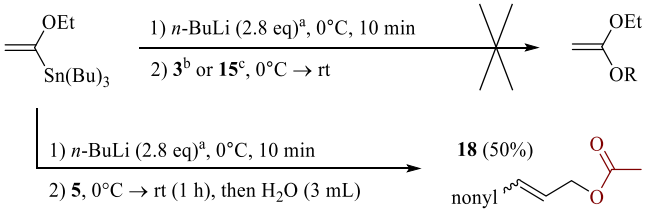
Table 1. Electrophile Preparation via Peroxidation of Trifluoromethanesulfonates[a]



[a]Values listed are isolated yields.

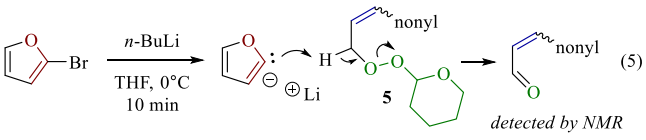
Scheme 1. Ketene Acetal Synthesis via Transmetalation of Nonheterocyclic Nucleophiles



[a]10 min or 2 h provided similar results. [b]Peroxide decomposition products observed. [c]Ketene acetal detected in trace amounts.

via transmetalation of a nonheterocyclic, tributylstannyl substrate. Although lithiation of the tributylstannyl starting material appeared to be successful (measured by the appearance of $Sn(Bu)_4$ in NMR), the resulting carbanion failed to react with a primary or bis monoperoxyacetal (**15** and **3**, respectively). Ketene acetal production, following transmetalation, occurred only in the presence of an allylic electrophile (**5**). The product, visualized with thin-layer chromatography (TLC), was hydrated upon workup and isolated as a stable ester (**18**) in moderate yield.

Early efforts to synthesize a ketene *O*,*O*-acetal from a simple, furan pronucleophile were unsuccessful, presumably due to enhanced volatility and preference for Kornblum–DeLaMare fragmentation by the resulting carbanion (eq 5).[28]



(5)

During preliminary investigations, α-heteroaryl carbanion formation, following metal–halogen[18a] or metal–proton[29] exchange, was optimized (see the Supporting Information for details). These experiments revealed that, although both methods were successful in generating the desired nucleophile (confirmed with methylation), deprotonation of benzofuran appears to be the most efficient route of lithiation at the α-position. Thus, with this in mind, electrophilic etherification was optimized using benzofuran-based pronucleophiles and a number of reaction condition combinations (Table 2).

Table 3 demonstrates the scope of ketene *O*,*O*-acetal synthesis using a benzofuran-derived, α-heteroaryl carbanion and monoperoxyacetal electrophiles. Etherification provided products in high yield by quantitative ^{1}H NMR (qNMR); ketene acetals were isolated in low to moderate, purified yields. Although the sp^2-hybridized nucleophile successfully reacted with primary substrates, experiments with secondary monoperoxyacetals resulted only in slow decomposition of the peroxide. Consistent with previous reports, C–O bond formation was characterized by transfer of the less hindered alkoxyl group to the heterocyclic nucleophile through selective displacement of the tetrahydropyranyloxy moiety from the electrophile.[17,19]

Table 4 summarizes the failure of 2-lithiobenzofuran to react with *tert*-butyl dialkyl peroxides despite manipulations in temperature, reaction times, and stoichiometric equivalents. In each case, nearly quantitative amounts of the peroxide starting material were recovered.

The inherent instability of aliphatic ketene acetals and their affinity for hydrolysis have been studied and recorded.[1] However, comparable reactivity of ketene acetals containing aryloxy substituents has been left unexplored. Thus, with this in mind, select, ketene *O*,*O*-acetal products (**19c–19e**) were

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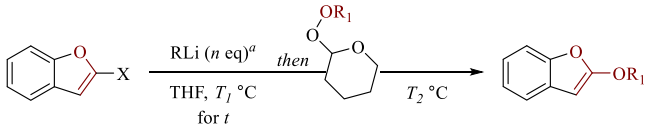
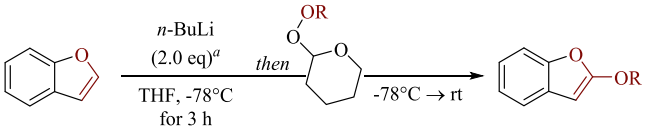
Table 2. Optimization of Electrophilic Etherification Using Benzofuran Pronucleophiles

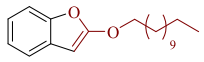
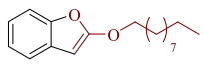
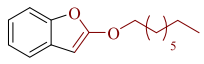
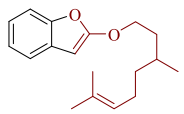
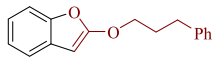
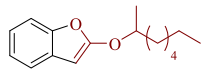


X	R	n	T_1 (°C)	t (h)	peroxide	T_2 (°C)	yield[b]
Br	*n*-Bu	1.1	0	3	**15**	0 → rt	nr
Br	*n*-Bu	0.4	0	2	**15**	0 → rt	trace
Br	*t*-Bu	2.0	−78 → rt	2	**16**	−78 → rt	34%[c]
H	*n*-Bu	1.3	−78 → rt	2	**14a**	−78	nr
H	*n*-Bu	1.3	−78 → rt	2	**14a**	−78 → 0	nr
H	*n*-Bu	1.3	−78	1	**14a**	−78 → rt	trace
H	*n*-Bu	0.5	−78	1.5	**13a**	−78 → rt	nr
H	*n*-Bu	2.1	−78	2	**14a**	−78 → rt	30%[c]
H	*n*-Bu	2.0	−78	3	**16**	−78 → rt	39%[c]

[a]Defined in comparison to 1 equiv of peroxide. [b]Values listed are crude yields unless otherwise stated. [c]These values were determined after workup using qNMR.

Table 3. Ketene *O,O*-Acetal Synthesis via Intermolecular Etherification



peroxide	product		crude yield[b]	isolated yield
12	**19a**		76%	39%
13a	**19b**		75%	54%
14a	**19c**		78%	46%
15a	**19d**		83%	34%
16	**19e**		81%	35%
17	**19f**		nr	nr

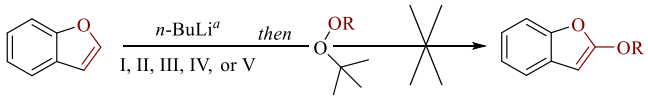
[a]3 h. [b]Yield determined prior to workup using qNMR.

mixed with water in the presence of catalytic H_2SO_4 for extended reaction periods at room temperature (Table 5).

Acid-catalyzed hydration of aryl ketene acetals provided a series of esters, derived from initial hemi-orthoester formation, in high yields. Breakdown of the hemi-orthoester intermediates was anticipated as the collapse of this moiety has been documented by other groups.[30]

Synthesis and Reactivity of *N,O* Ketene Acetals. Etherification between α-heteroaryl carbanions and electrophilic peroxides was applied to the synthesis of ketene *N,O*-acetals. As illustrated in Table 6, lithiated, indole-based substrates readily reacted with primary monoperoxyacetals to provide desired products in modest to good, isolated yields.

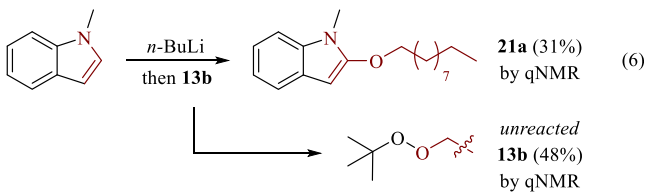
Table 4. Attempted Ketene Acetal Synthesis Using Dialkyl Peroxide Electrophiles



entry	peroxide (equiv)	temperature (°C)	time
I	**14b** (1.2)[b]	−78	4 h
II	**14b** (1.2)[b]	−78 → 0	4 h
III	**14b** (1.2)[b]	−78 → rt	overnight
IV	**13b** (1.0)[c]	−78 → rt	overnight
V	**13b** (1.0)[d]	−78 → rt	overnight

[a]2 h; −78 °C → rt. [b]Carbanion eq: 1.0. [c]Carbanion eq: 1.1. [d]Carbanion eq: 2.0.

Additionally, contrary to its oxygen homologue, lithiated indole reacted with a secondary monoperoxyacetal (**22**) and a *tert*-butyl dialkyl peroxide (eq 6) with moderate success.



(6)

The addition of an electron-donating group ($-OCH_3$) to the pronucleophile produced no significant change in ketene *N,O*-acetal production (Table 6, **23a−23c**), while the addition of an electron-withdrawing group ($-NO_2$) to the same molecule provided no desired product (eq 7). Rather, induced electron deficiency (per nitro group in position 6) of the indole nucleus activated nucleophilic aromatic substitution of *n*-BuLi to the heterocycle (at position 7);[31,32] under these conditions, the peroxide underwent base-promoted Kornblum−DeLaMare fragmentation, as opposed to alkoxy transfer.[28]

Table 7 outlines the extension of ketene *N,O*-acetal synthesis to intermolecular reactions between α-pyridinyl carbanions and monoperoxyacetals. Following metal−halogen exchange, lithiated pyridine consumed primary, peroxide

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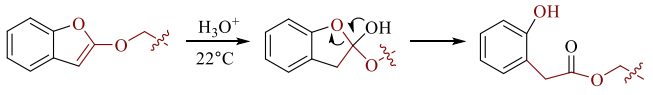
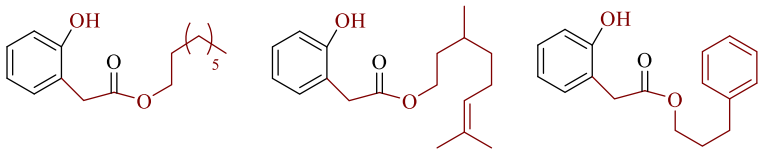
Table 5. Acid-Catalyzed Hydration of Ketene *O,O*-Acetals to Stable Esters[a]



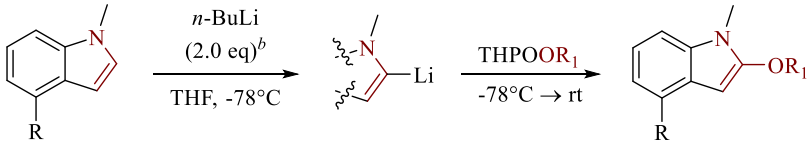
ketene *O,O*-acetal **19c-19e** | *hemi-orthoester intermediate* | ester product **20a-20c**



20a (87%) | **20b** (84%) | **20c** (83%)

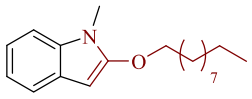
[a]Values listed are isolated yields.

Table 6. Ketene *N,O*-Acetal Synthesis via α-Indolyl Carbanions and Monoperoxyacetals[a]

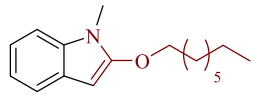


1-methylindole: R = H
4-methoxy-1-methylindole: R = OCH_3

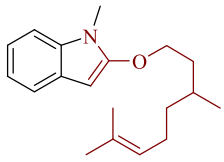
21a-c, 22
23a-c



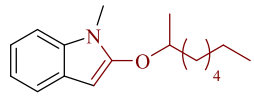
21a[c] (75%)



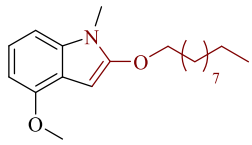
21b (71%)



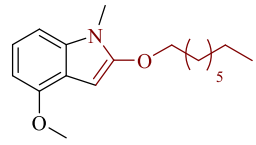
21c (73%)



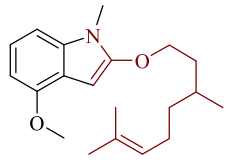
22 (35%)



23a (71%)



23b (75%)



23c (78%)

[a]Values listed are isolated yields unless otherwise stated. [b]3 h. −78 °C → rt. [c]This product was found to be in quantitative yield prior to workup (qNMR).

electrophiles within 30 min and provided products in high yields (**25a−25c**); the same nucleophile generated a ketene *N,O*-acetal derived from a secondary monoperoxyacetal with only moderate success (**25d**). Interestingly, similar to sp^2-hybridized, ether carbanions (Table 4) and contrary to indole-based nucleophiles (Table 6), lithiated pyridine failed to react with a *tert*-butyl dialkyl peroxide. Upon the addition of an electron-donating group onto the pyridine pronucleophile, yields of ketene *N,O*-acetal products remained fairly unchanged (CH_3 in position 4, **26a−c**) or were enhanced on average (OCH_3 in position 6, **27a−c**). Similar to that observed with indole molecules, pyridine substrates bearing an electron-withdrawing group (NO_2) in position 3 or position 4 failed to react with a monoperoxyacetal (Table 7, **28a**, **28b**). As

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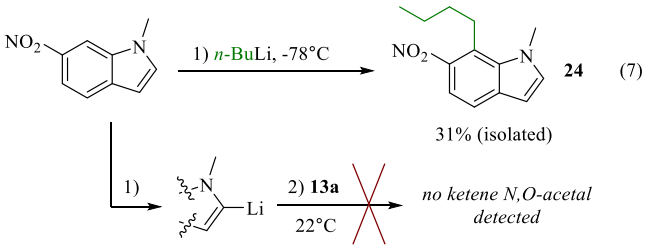
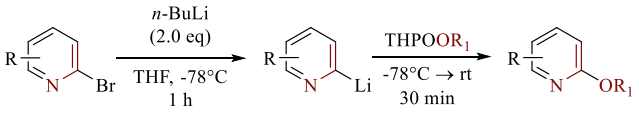
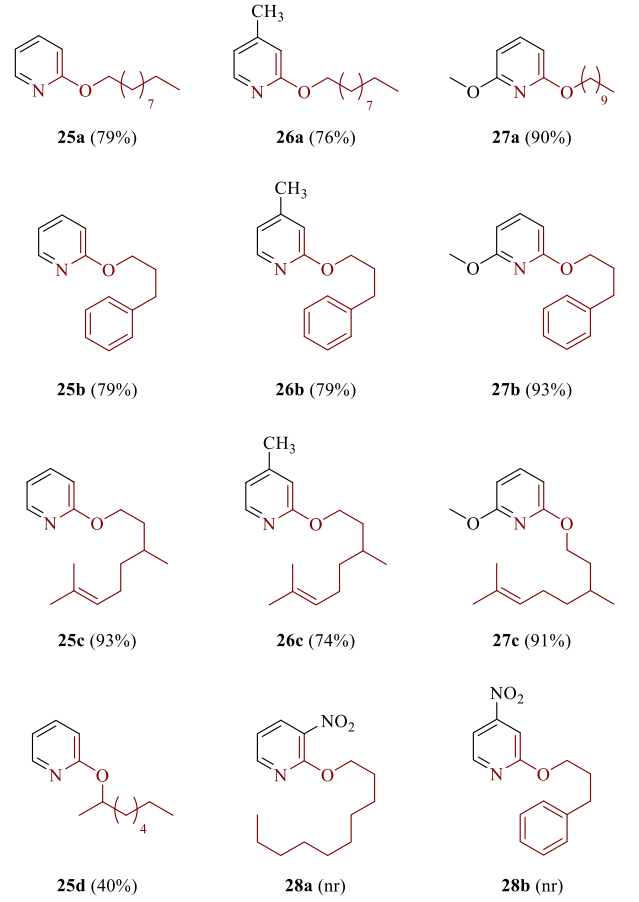


Table 7. Ketene *N,O*-Acetal Synthesis via Lithiated Pyridines and Monoperoxyacetals[a]



2-bromopyridine: R = H (pos 3-6)	**25a-d**
2-bromo-4-methylpyridine: R = CH_3 (pos 4)	**26a-c**
2-bromo-6-methoxypyridine: R = OCH_3 (pos 6)	**27a-c**
2-bromo-3-nitropyridine: R = NO_2 (pos 3)	**28a**
2-bromo-4-nitropyridine: R = NO_2 (pos 4)	**28b**

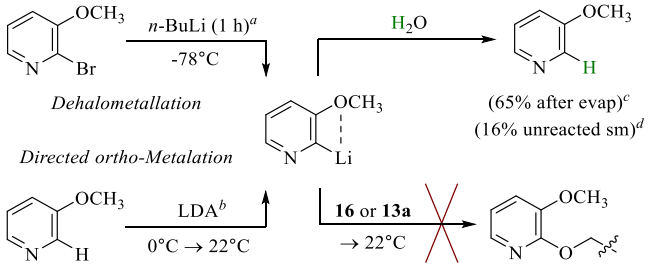


[a]Isolated yields are listed for all products.

anticipated, the addition of a nitro group to the pyridine system activated the heterocycle toward nucleophilic aromatic substitution,[33] leaving a large amount of the peroxide starting material unreacted.

Efforts to react an α-heteroaryl carbanion, bearing an electron-donating substituent in the β (or 3)-position, with monoperoxyacetals were unsuccessful (Scheme 2). Generation of the β-occupied carbanion was found to be successful,

Scheme 2. Attempted Ketene *N,O*-Acetal Synthesis with a β-Position EDG

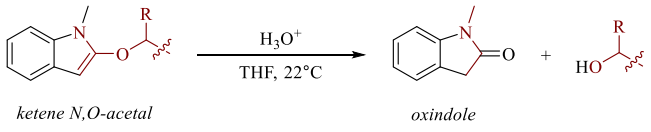


[a]2 h provided similar results. [b]Prepared *in situ* from diisopropylamine and *n*-BuLi at 0 °C (30 min). [c,d]Determined using qNMR.

however, as the volatile product of exchange—3-methoxypyridine—was present (in a 4:1 ratio, relative to the starting material) following aqueous quench and evaporation. Thus, the failure of the nucleophile to react with electrophiles was presumably due to steric constraints introduced at the adjacent β-position.

To gauge the reactivity of indole-based, ketene *N,O*-acetals, select products were subjected to acid-catalyzed hydration at room temperature (Table 8). Within hours, ketene *N,O*-acetals

Table 8. Acid-Catalyzed Hydration of Ketene *N,O*-Acetals to Oxindoles



21b: R = H (*from primary electrophile*)
22: R = CH_3 (*from secondary electrophile*)
29

substrate	R	time (h)	oxindole (yield)	alcohol (yield)
21b	H	6	**29** (44%)	octanol (42%)
22	CH_3	10	**29** (51%)[a]	2-octanol (43%)[a]

[a]Yield determined using qNMR.

bearing a primary (**21b**) or secondary (**22**) alkoxy group were completely hydrolyzed to an oxindole (**29**) (and a corresponding alcohol) in moderate yield. This conversion, from indole to oxindole, provides therapeutic potential as the latter moiety has served as a core structure in a large number of drug discovery pursuits.[34,35]

DISCUSSION

While the production of silyl ketene acetals is nearly routine,[2−7,9b,c] methods for the synthesis of alkyl, ketene *O,O*- and *N,O*-acetals are underdeveloped.[1] Moreover, isolation of nonsilylated products is challenging, as few reports of doing so exist.[7,11−13] Herein, we report a novel route to stabilized, heteroaromatic ketene acetals via etherification of α-heteroaryl carbanions and monoperoxyacetals. Although the transfer of electrophilic alkoxyl to sp^2-hybridized nucleophiles has been documented,[17,22] to our knowledge, no attention has been given to the use of this method to form ketene acetals.

The failure to isolate aliphatic ketene acetals formed from a simple enol ether nucleophile (Scheme 1) was not surprising, as these products are too reactive to withstand workup or purification.[14] However, through the use of a more stable pronucleophile, the characterization of etherification products

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was feasible. By virtue of their stability, heteroaromatic compounds provide a unique scaffold for the creation of otherwise unstable, ketene acetal products.[36,37] Along these lines, the benefits of our reported method are twofold: (1) aromatic substrates allow for the efficient isolation of functionalized products in modest (ketene *O,O*-acetals, Table 3) to high (ketene *N,O*-acetals, Tables 6 and 7) yields and (2) the use of biologically relevant substructures offers a direct opportunity for adding C−O bonds to a large number of natural products.[34,38]

The highest electrophilic etherification yields were obtained from ketene *N,O*-acetal synthesis with lithiated pyridine (Table 7), while the lowest yields of the same reaction were observed during ketene *O,O*-acetal synthesis with lithiated benzofuran (Table 3). Thus, variances in ketene acetal synthesis are seemingly related to the strength of the α-heteroaryl nucleophile. Based on our results, pyridine-based carbanions appear to be the most reactive toward electrophilic peroxide and are therefore the strongest nucleophiles, which align with reported pK_a values (Figure 3).[39] Differences in carbanion

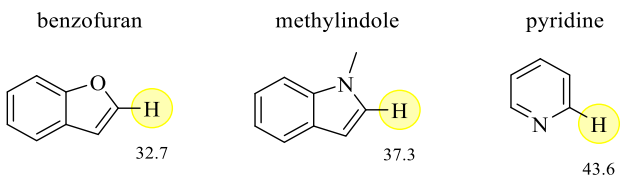

Figure 3. Reported pK_a values for benzofuran, methylindole, and pyridine.

reactivity by pK_a may also account for the failed synthesis of ketene *O,O*-acetals from secondary monoperoxyacetal electrophiles (Table 3), as ketene *N,O*-acetals were obtained from the same type of electrophile with more nucleophilic carbanions (methylindole: Table 6; pyridine: Table 7).

Products derived from benzofuran (Table 3) were the most susceptible to decomposition during workup or purification. According to previous reports, the superior, isolated yields of ketene *N,O*-acetals in comparison to ketene *O,O*-acetals may have resulted from increased aromaticity of products arising from nitrogen-containing heterocycles.[40−48] Benzofuran reportedly has a lower degree of aromaticity compared to methylindole and pyridine.[40]

Lastly, the differences in ketene acetal synthesis between monoperoxyacetal and dialkyl peroxide electrophiles were anticipated and can be attributed to the previously noted, enhanced reactivity of monoperoxyacetals toward unstabilized carbanions.[17]

CONCLUSIONS

Intermolecular etherification between α-heteroaryl carbanions and electrophilic peroxides provides an unexplored yet efficient route to isolable, alkyl ketene acetals. The use of heteroaromatic pronucleophiles confers added stability to an otherwise reactive class of compounds and provides a facile method of adding alkoxy groups to some important substructures in nature. Isolated yields ranged from moderate to excellent, with variations attributed to varying pK_a values per pronucleophile at the α-position and ultimate product aromaticity. Monoperoxyacetal electrophiles proved to be much more reactive compared to *tert*-butyl dialkyl peroxides; 2-lithioindoles were the only sp^2-hybridized nucleophiles that underwent C−O bond formation with a simple, peroxide electrophile. The method developed herein overcomes the typical challenges associated with the instability of alkyl, ketene acetals as products formed from etherification were produced in satisfying yields, withstood purification, and demonstrated an ability to be used in further synthesis, following isolation.

EXPERIMENTAL SECTION

General Experimental Section. *Synthesis.* All synthetic experiments were performed in flame-dried glassware and in an inert atmosphere of N_2 unless otherwise stated. Reaction temperatures were controlled using various mixtures: −78 °C (solid CO_2/acetone), 0 °C (ice/water), and greater than 22 °C (synthetic oil/hot plate).

Solvents/Reagents. Solvents were either (i) purchased as anhydrous [dimethylformamide (DMF), ether] solvents and used without modification or (ii) freshly distilled in our laboratory [tetrahydrofuran (THF), dichloromethane (DCM)]. THF was distilled from benzophenone and sodium; DCM was distilled from calcium hydride. All reagents were used as purchased unless otherwise noted.

Chromatography. TLC was conducted on 175−225 μm thick, aluminum-backed, silica gel 60 plates coated with a fluorescent indicator, F_{254}. TLC experiments were analyzed using a handheld UV lamp and/or developed with one of the following stains: 1% ammonium cerium sulfate dihydrate, 2.5% ammonium molybdate tetrahydrate, and 10% concd H_2SO_4 in H_2O (useful for most compounds, heat required); 1% *N,N′*-dimethyl-*p*-phenylenediamine in 1 mL of CH_3COOH, 20 mL of H_2O, and 100 mL of MeOH (especially useful for peroxides; hydroperoxides exhibit a bright, pink color without heat, and dialkyl peroxides/monoperoxyacetals require heat); 1% $KMnO_4$ in H_2O (useful for alkenes and/or conjugated systems, heat required for some molecules). Flash column chromatography was performed using high-purity-grade silica gel (60 Å pore size, 230−400 mesh particle size).

Characterization. NMR spectroscopy was performed at a frequency of 600 MHz (^{1}H NMR) and 150 MHz (^{13}C{^{1}H} NMR). As noted, all spectra (^{1}H NMR or ^{13}C{^{1}H} NMR) were obtained using $CDCl_3$ or C_6D_6 as the solvent (some ketene acetal products were reactive with $CDCl_3$). Spectral data for all compounds are written as (signal multiplicity, coupling constant(s) (*J*), number of protons). High-resolution mass spectrometry (HRMS) was performed using electrospray ionization (ESI) on a Bruker SolariX FT-ICR by the Nebraska Center for Mass Spectrometry at the University of Nebraska−Lincoln.

Quantitative ^{1}H NMR Analysis. Due to the inherent reactivity of ketene acetals (*O,O* or *N,O*) throughout workup, purification, and extended storage, qNMR was performed to provide insight on overall reaction completion/success. Where noted, an internal standard (1-undecene or toluene) was used according to the following: an oven-dried, NMR tube was charged with a measured amount of the internal standard (30.0−60.0 mg) and deuterated solvent (C_6D_6). Under the protection of nitrogen, an aliquot of crude solution was drawn from the reaction flask, weighed, and added to the sample tube. The analyte/internal standard mixture was promptly analyzed with ^{1}H NMR spectroscopy; qNMR yields were determined using a known calculation method (see "Quantitative NMR", provided by Sigma-Aldrich).

2-Hydroperoxy-tetrahydro-2H-pyran (1).[17] A round-bottom flask with a magnetic stir bar was cooled to 0 °C and flushed with nitrogen. Once chilled, the flask was charged with 50% (w/w) aqueous hydrogen peroxide (6.66 mL, 118 mmol) and a catalytic amount of 10% aq sulfuric acid (0.1 mL). The resulting mixture was stirred for 15 min, whereupon 3,4-dihydro-2*H*-pyran (5.40 mL, 5.00 g, 58.8 mmol) was introduced into the reaction, neat and dropwise for 10 min. The reagents reacted over 1 h at 0 °C before being diluted with saturated, aqueous ammonium chloride (approx. 15 mL). The aqueous and organic layers were separated; the aqueous layer was washed with EtOAc (3 × 30 mL) and the organic layer was washed with ammonium sulfate (2 × 65 mL) sequentially. The collected

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organics were dried over sodium sulfate, filtered, and concentrated *in vacuo* at 40 °C. The obtained residue was purified via flash column chromatography (10−25% EtOAc/Hex) to provide THP hydroperoxide as a viscous, colorless oil (5.979 g, 86%). Characterization: R_f = 0.20 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.30−9.09 (m, 1H), 5.09 (dd, J = 4.67, 3.04 Hz, 1H), 3.99 (ddd, J = 11.31, 8.11, 3.27 Hz, 1H), 3.69−3.63 (m, 1H), 1.83−1.71 (2H), 1.69−1.52 (4H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 102.6, 62.9, 27.4, 25.0, 19.6.

*tert-Butyl Hydroperoxide (**2**) [CAS#: 75-91-2].* Provided by Sigma-Aldrich, this hydroperoxide was obtained as a 5.0−6.0 M solution in decane. *tert*-Butyl hydroperoxide was utilized in dialkyl peroxide synthesized as purchased.

*2,2′-Peroxybis(tetrahydro-2H-pyran) (**3**, Eq 3).*[17,23] A round-bottom flask with a magnetic stir bar was flame-dried, placed under vacuum, and cooled to 0 °C. Once chilled, the flask was charged with 3,4-dihydropyran (0.710 g, 8.50 mmol) and THP hydroperoxide (**1**, 1.00 g, 8.50 mmol). The system was flushed with N_2, whereupon 10% (v/v) sulfuric acid in THF (42.0 μL, 0.79 mmol) was introduced into the reaction slowly. The stirring solution was warmed to room temperature over 1 h before being diluted with 10% EtOAc/Hex (approx. 10 mL). The crude mixture was washed with water (approx. 3 mL), and the resulting layers were separated. The aqueous layer was extracted with EtOAc (3×); the collected organics were dried over sodium sulfate, filtered, and concentrated in vacuo at 40 °C. The obtained residue was purified via flash column chromatography (4% EtOAc/Hex) to afford the bisperoxyacetal as a colorless oil (1.415 g, 83%). Characterization: R_f = 0.31 (10% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.19 (t, J = 3.66 Hz, 0.64H), 5.13 (dd, J = 3.60, 3.23 Hz, 1.23H), 4.03 (ddd, J = 11.88, 9.42, 2.99 Hz, 1.30H), 3.93 (ddd, J = 11.35, 8.33, 3.03 Hz, 0.69H), 3.59−3.50 (m, 2H), 1.75−1.63 (4H), 1.63−1.41 (8H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 101.8, 100.3, 62.5, 62.2, 27.9, 27.7, 25.2, 25.1, 19.6, 19.4.

*(E/Z)-1-Bromododec-2-ene (**4**, Eq 4).*[49] A dual-necked, round-bottom flask with a magnetic stir bar was flame-dried, equipped with a reflux condenser, and placed under vacuum. Once evacuated, the flask was charged with anhydrous DCM (80 mL). The system was flushed with N_2, whereupon allyl bromide (425.0 μL, 0.591 g, 4.80 mmol) was injected into the solution. The resulting mixture was stirred for 5 min before 1-undecene (2.50 g, 16.0 mmol) and the Grubbs Second Generation catalyst (67.9 mg, 0.08 mmol, in 1 mL of DCM) was introduced into the flask. Upon addition of all reagents, the reaction was allowed to reflux at a constant temperature (95 °C). Following the disappearance of the starting material (TLC, approx. 9 h), the crude was cooled to room temperature and concentrated in vacuo at 40 °C. The obtained residue was purified via flash column chromatography (hexane) to furnish the allylic bromide (**4**) as a colorless oil (1.094 g, 92%). 1-Bromododec-2-ene was isolated as an inseparable mixture of E/Z isomers. Characterization: R_f = 0.56 (Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ (both isomers) 5.81−5.74 (m, 1H), 5.68 (dtt, ^3J = 7.56, ^3J = 15.09, ^4J = 1.37 Hz, 1H), 4.00 (d, J = 8.36 Hz, 0.31H), 3.95 (d, J = 7.55 Hz, 1.69H), 2.16−2.10 (m, 0.31H), 2.09−2.02 (m, 1.69H), 1.41−1.34 (2H), 1.33−1.20 (12 H), 0.88 (t, J = 7.14 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (major isomer) 136.8, 126.2, 33.7, 32.1, 31.9, 29.5, 29.3, 29.1, 28.8, 22.7, 14.1.

General Procedure for Silver(I) Oxide Synthesis (Ag_2O).[50] A 50 mL beaker, with a magnetic stir bar, was charged with silver nitrate (1.0 equiv, 883. mg, 5.20 mmol) and water (20 mL). The salt was completely dissolved, whereupon sodium hydroxide (1.0 equiv, 1.04 mL, 5.20 mmol, 5.00 N) was added dropwise into the solution, resulting in an instantaneous formation of a black precipitate. The mixture was stirred vigorously for 15 min before being allowed to settle for another 5 min. The beaker was filtered, and the trapped solid was washed with several aliquots of water, absolute ethanol, and ether. The Ag_2O was transferred to a scintillation vial and dried to a constant mass under high vacuum (approx. 4 h) at 110 °C to furnish freshly prepared silver(I) oxide as a fine, black powder (580.0 mg, 96%). This reagent was stored in the dark and used in further synthesis within an hour after production.

*(E/Z)-2-(Dodec-2-en-1-ylperoxy)tetrahydro-2H-pyran (**5**, Eq 4).*[17,24] A round-bottom flask with a magnetic stir bar was flame-dried and charged with freshly prepared silver(I) oxide (278.0 mg, 1.20 mmol). The flask was capped with a rubber septum and placed under vacuum, whereupon anhydrous ethyl acetate (dried with sodium sulfate, 5 mL) was injected to suspend the black powder. The system was evacuated once more before being flushed with N_2. Upon mixture homogeneity, solutions of THP hydroperoxide (**1**, 118.0 mg, 1.00 mmol) and allylic bromide (**4**, 247.0 mg, 1.00 mmol) in minimal EtOAc were introduced into the reaction sequentially. All syringes were flushed into the flask with EtOAc (2 × 0.5 mL). After stirring at room temperature for approx. 6 h, the disappearance of the starting material was observed (TLC), and the reaction material was poured through a plug of Celite. The filtered residue was washed with several aliquots of EtOAc (20 mL) and concentrated in vacuo at 30 °C. The crude was purified via flash column chromatography (Hex-3% EtOAc/Hex) to provide the unsaturated monoperoxyacetal as a colorless oil (327.4 mg, 54%). (*E/Z*)-2-(Dodec-2-en-1-ylperoxy)-tetrahydro-2*H*-pyran was isolated as an inseparable mixture of E/Z isomers. Characterization: R_f = 0.36 (5% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ (both isomers) 5.82−5.76 (m, 1H), 5.62−5.56 (dtt, ^3J = 6.72, ^3J = 13.51, ^4J = 1.43 Hz, 1H), 5.17 (dd, J = 4.07, 3.15 Hz, 1H), 4.65 (dt, ^3J = 6.78, ^5J = 1.50 Hz, 0.16H), 4.52 (dd, J = 6.78, 0.75 Hz, 1.86H), 4.02 (ddd, J = 11.49, 8.70, 3.03 Hz, 1H), 3.66−3.61 (m, 1H), 2.13−2.02 (m, 2H), 1.79−1.69 (2H), 1.68−1.51 (4H), 1.42−1.34 (2H), 1.34−1.19 (12H), 0.88 (t, J = 7.18 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (major isomer) 137.9, 123.7, 100.8, 76.3, 62.5, 32.4, 31.9, 29.6, 29.5, 29.3, 29.2, 28.9, 27.8, 25.2, 22.7, 19.6, 14.1.

*General Procedure for Trifluoromethanesulfonate Synthesis (Table 1, **6**−**11**).*[17,19,25] A round-bottom flask was flame-dried, placed under vacuum, and cooled to 0 °C. Once chilled, the flask was charged with 60.0 mL of anhydrous DCM and evacuated once more. The system was flushed with N_2, whereupon an alcohol (1.00 equiv, 20.0 mmol), triflic anhydride (1.40 equiv, 28.0 mmol), and 2,6-lutidine (1.45 equiv, 29.0 mmol) were introduced into the flask sequentially. The resulting mixture was stirred for 20 min before being diluted with ice-cold potassium bisulfate (0.10 M, approx. 50 mL) and ice-cold hexanes (approx. 75 mL). The solution's layers were separated, and the aqueous layer was washed with ice-cold hexanes (3 × 50 mL). The collected organics were dried with sodium sulfate, filtered, and concentrated in vacuo at room temperature to furnish a quantitative yield (for most cases, lower yields were observed for chiral products) of the desired alkyl trifluoromethanesulfonate as a tea-brown oil. Trifluoromethanesulfonates were stored in a −20 °C freezer and used for monoperoxyacetal/dialkyl peroxide synthesis immediately after production/characterization.

*Dodecyl trifluoromethanesulfonate (**6**).* By following the general procedure for trifluoromethanesulfonate synthesis as described above, 1-dodecanol (2.092 g, 11.0 mmol) was reacted with triflic anhydride (2.66 mL, 4.434 g, 15.4 mmol) and 2,6-lutidine (1.87 mL, 1.727 g, 16.0 mmol) to provide dodecyl trifluoromethanesulfonate as a tea-brown oil (3.467 g, 99%). Characterization: ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.44 (t, J = 6.49 Hz, 2H), 1.73 (tt, J = 7.55, 6.56 Hz, 2H), 1.37−1.29 (m, 2H), 1.28−1.10 (16H), 0.79 (t, J = 7.16 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 118.7 (q, $^2J_{C-F}$ = 323.7 Hz), 77.8, 31.9, 29.6, 29.5, 29.3, 29.2, 28.9, 25.1, 22.7, 14.1.

*Decyl Trifluoromethanesulfonate (**7**).* By following the general procedure for trifluoromethanesulfonate synthesis as described above, 1-decanol (3.86 mL, 3.198 g, 20.0 mmol) was reacted with triflic anhydride (4.83 mL, 8.061 g, 28.0 mmol) and 2,6-lutidine (3.40 mL, 3.139 g, 29.0 mmol) to provide decyl trifluoromethanesulfonate as a tea-brown oil (5.652 g, 97%). Characterization: ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.44 (t, J = 6.56 Hz, 2H), 1.73 (tt, J = 7.56, 6.47 Hz, 2H), 1.36−1.29 (m, 2H), 1.28−1.12 (12H), 0.79 (t, J = 7.16 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 118.7 (q, $^2J_{C-F}$ = 319.53 Hz), 77.8, 31.8, 29.4, 29.3, 29.2, 29.2, 28.8, 25.0, 22.6, 14.0.

*Octyl Trifluoromethanesulfonate (**8**).* By following the general procedure for trifluoromethanesulfonate synthesis as described above, 1-octanol (3.20 mL, 2.631 g, 20.0 mmol) was reacted with triflic

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anhydride (4.83 mL, 8.061 g, 28.0 mmol) and 2,6-lutidine (3.40 mL, 3.139 g, 29.0 mmol) to provide octyl trifluoromethanesulfonate as a tea-brown oil (1.258 g, 96%). Characterization: ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.44 (t, J = 6.57 Hz, 2H), 1.73 (tt, J = 7.29, 6.53 Hz, 2H), 1.37−1.29 (m, 2H), 1.28−1.12 (8H), 0.79 (t, J = 7.19 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 118.7 (q, $^2J_{C-F}$ = 320.14 Hz), 77.8, 31.7, 29.2, 29.0, 28.8, 25.1, 22.6, 14.1.

*3,7-Dimethyl-6-octenyl Trifluoromethanesulfonate (**9**).* By following the general procedure for trifluoromethanesulfonate synthesis as described above, 3,7-dimethyl-6-en-1-ol (4.80 mL, 4.100 g, 25.0 mmol) was reacted with triflic anhydride (5.91 mL, 9.870 g, 35.0 mmol) and 2,6-lutidine (4.20 mL, 3.880 g, 36.3 mmol) to provide 3,7-dimethyl-6-octenyl trifluoromethanesulfonate as a tea-brown oil (6.611 g, 92%). Characterization: ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.90 (tsept, ^3J = 7.17, ^4J = 1.51 Hz, 1H), 4.46−4.36 (m, 2H), 1.90−1.75 (m, 2H), 1.75−1.66 (m, 1H), 1.57−1.53 (m, 1H), 1.52 (s, 3H), 1.50−1.44 (m, 1H), 1.43 (s, 3H), 1.22−1.15 (m, 1H), 1.15−1.07 (m, 1H), 0.78 (d, J = 6.35 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 131.9, 124.0, 118.7 (q, $^2J_{C-F}$ = 319.26 Hz), 76.2, 36.6, 36.0, 28.7, 25.7, 25.2, 19.1, 17.7.

*3-Phenylpropyl Trifluoromethanesulfonate (**10**).* By following the general procedure for trifluoromethanesulfonate synthesis as described above, 3-phenylpropan-1-ol (2.08 mL, 2.080 g, 15.0 mmol) was reacted with triflic anhydride (3.62 mL, 6.050 g, 21.0 mmol) and 2,6-lutidine (2.50 mL, 2.331 g, 21.8 mmol) to provide 3-phenylpropyl trifluoromethanesulfonate as a tea-brown oil (3.952 g, 98%). Characterization: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25−7.19 (m, 2H), 7.16−7.12 (m, 1H), 7.11−7.07 (m, 2H), 4.44 (t, J = 6.29 Hz, 2H), 2.68 (t, J = 7.53 Hz, 2H), 2.06 (tt, J = 7.54, 6.27 Hz, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 118.7 (q, $^2J_{C-F}$ = 319.25 Hz), 139.5, 128.7, 128.4, 126.6, 76.5, 31.1, 30.8.

*Octan-2-yl Trifluoromethanesulfonate (**11**).* Note: Longer reaction times (1−2 h) were required for the synthesis of this molecule. By following the general procedure for trifluoromethanesulfonate synthesis as described above, 2-octanol (503.0 mg, 3.75 mmol) was reacted with triflic anhydride (905.0 μL, 1.511 g, 5.25 mmol) and 2,6-lutidine (636.0 μL, 589.0 mg, 5.44 mmol) to provide octan-2-yl trifluoromethanesulfonate as a tea-brown oil (800.0 mg, 81%). Characterization: ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.02−4.95 (tq, J = 6.24, 6.30 Hz, 1H), 1.77−1.69 (m, 1H), 1.65−1.56 (m, 1H), 1.42 (d, J = 6.30 Hz, 3H), 1.38−1.11 (8H), 0.80 (t, J = 6.79 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 90.0, 36.7, 31.5, 28.8, 24.7, 22.5, 21.1, 14.0.

General Procedure for Monoperoxyacetal and Dialkyl Peroxide Synthesis via Trifluoromethanesulfonates (Table 1, 12−17).[17,19,25] A round-bottom flask with a magnetic stir bar was flame-dried and charged with potassium *tert*-butoxide (1.00 equiv, 10.0 mmol). The flask was capped with a rubber septum, placed under vacuum, and cooled to 0 °C. Once chilled, anhydrous THF (50 mL) was injected and the resulting mixture was allowed to stir for several minutes. The system was evacuated once more before being flushed with N_2. Upon solution homogeneity, an aliquot of hydroperoxide (**1** or **2**, 1.00 equiv, 10.0 mmol) was introduced into the reaction. The combined reagents were stirred for 3 min at 0 °C, whereupon freshly prepared trifluoromethanesulfonate (**6**, **7**, **8**, **9**, **10**, or **11**, 1.00 equiv, 10.0 mmol) was obtained from the −20 °C freezer and added dropwise for 10 min (molecule added neat). After stirring for 25 min at 0 °C, the reaction mixture was quenched with water (approx. 20 mL) and extracted with 10% EtOAc/Hex (3 × 25 mL). The collected organics were dried over sodium sulfate, filtered, and concentrated in vacuo at 30 °C. Obtained residues were purified via flash column chromatography (1% EtOAc/Hex) to provide monoperoxyacetals and dialkyl peroxides as colorless oils in modest to excellent yields.

*2-(Dodecylperoxy)tetrahydro-2H-pyran (**12**).* By following the general procedure for monoperoxyacetal synthesis using trifluoromethanesulfonates as described above, dodecyl trifluoromethanesulfonate (**6**, 3.184 g, 10.0 mmol) was reacted with THP hydroperoxide (**1**, 1.181 g, 10.0 mmol) and potassium *tert*-butoxide (1.122 g, 10.0 mmol) to provide the title electrophile as a colorless oil (2.796 g, 98%). Characterization: R_f = 0.47 (5% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.08 (dd, J = 4.13, 3.10 Hz, 1H), 4.02 (t, J = 6.75 Hz, 2H), 3.95 (ddd, J = 11.36, 8.32, 2.86 Hz, 1H), 3.59−3.53 (m, 1H), 1.72−1.62 (2H), 1.60−1.43 (6H), 1.33−1.26 (2H), 1.26−1.14 (16H), 0.81 (t, J = 7.17 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 100.8, 75.4, 62.6, 31.9, 29.7, 29.6, 29.6, 29.5, 29.4, 29.4, 28.0, 27.9, 26.0, 25.2, 22.7, 19.7, 14.1.

*2-(Decylperoxy)tetrahydro-2H-pyran (**13a**).* By following the general procedure for monoperoxyacetal synthesis using trifluoromethanesulfonates as described above, decyl trifluoromethanesulfonate (**7**, 1.843 g, 6.35 mmol) was reacted with THP hydroperoxide (**1**, 750.0 mg, 6.35 mmol) and potassium *tert*-butoxide (712.0 mg, 6.35 mmol) to provide the title electrophile as a colorless oil (1.476 g, 90%). Characterization: R_f = 0.46 (5% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.15 (dd, J = 4.15, 3.19 Hz, 1H), 4.09 (t, J = 6.81 Hz, 2H), 4.02 (ddd, J = 11.37, 8.40, 2.98 Hz, 1H), 3.66−3.60 (m, 1H), 1.80−1.69 (2H), 1.68−1.51 (6H), 1.42−1.33 (2H), 1.33−1.19 (12H), 0.88 (t, J = 7.17 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 100.8, 75.4, 62.5, 31.9, 29.5, 29.4, 29.3, 27.9, 27.8, 26.0, 25.2, 22.7, 19.7, 14.1.

*1-(tert-Butylperoxy)decane (**13b**).* By following the general procedure for dialkyl peroxide synthesis using trifluoromethanesulfonates as described above, decyl trifluoromethanesulfonate (**7**, 4.021 g, 13.9 mmol) was reacted with *tert*-butyl hydroperoxide (**2**, 2.77 mL, 1.248 g, 13.9 mmol) and potassium *tert*-butoxide (1.586 g, 13.9 mmol) to provide the title electrophile as a colorless oil (3.069 g, 96%). Characterization: R_f = 0.77 (5% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.96 (t, J = 6.76 Hz, 2H), 1.61 (tt, J = 7.94, 6.78 Hz, 2H), 1.42−1.28 (14H), 1.27 (s, 9H), 0.91 (t, J = 7.16 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 80.0, 75.2, 31.9, 29.6, 29.6, 29.5, 29.3, 27.9, 26.3, 26.2, 22.7, 14.1.

*2-(Octylperoxy)tetrahydro-2H-pyran (**14a**).* By following the general procedure for monoperoxyacetal synthesis using trifluoromethanesulfonates as described above, octyl trifluoromethanesulfonate (**8**, 1.310 g, 5.00 mmol) was reacted with THP hydroperoxide (**1**, 591.0 mg, 5.00 mmol) and potassium *tert*-butoxide (561.0 mg, 5.00 mmol) to provide the title electrophile as a colorless oil (999.0 mg, 87%). Characterization: R_f = 0.47 (5% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.05 (dd, J = 4.18, 3.20 Hz, 1H), 3.99 (t, J = 6.78 Hz, 2H), 3.92 (ddd, J = 11.39, 8.16, 2.88 Hz, 1H), 3.57−3.50 (m, 1H), 1.70−1.59 (2H), 1.58−1.41 (6H), 1.31−1.24 (2H), 1.24−1.11 (8H), 0.78 (t, J = 7.18 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 100.8, 75.4, 62.2, 31.8, 29.4, 29.2, 28.0, 27.9, 26.0, 25.2, 22.7, 19.7, 14.1.

*1-(tert-Butylperoxy)octane (**14b**).* By following the general procedure for dialkyl peroxide synthesis using trifluoromethanesulfonates as described above, octyl trifluoromethanesulfonate (**8**, 2.623 g, 10.0 mmol) was reacted with *tert*-butyl hydroperoxide (**2**, 2.00 mL, 901. mg, 10.0 mmol) and potassium *tert*-butoxide (1.122 g, 10.0 mmol) to provide the title electrophile as a colorless oil (1.742 g, 86%). Characterization: R_f = 0.77 (5% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.94 (t, J = 6.75 Hz, 2H), 1.60 (tt, J = 8.06, 6.75 Hz, 2H), 1.42−1.27 (10H), 1.26 (s, 9H), 0.90 (t, J = 7.18 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 80.0, 75.1, 31.8, 29.5, 29.2, 27.9, 26.3, 26.2, 22.6, 14.1.

*2-((3,7-Dimethyloct-6-en-1-yl)peroxy)tetrahydro-2H-pyran (**15**).* By following the general procedure for monoperoxyacetal synthesis using trifluoromethanesulfonates as described above, 3,7-dimethyl-6-octenyl trifluoromethanesulfonate (**9**, 1.980 g, 6.85 mmol) was reacted with THP hydroperoxide (**1**, 809.0 mg, 6.85 mmol) and potassium *tert*-butoxide (769.0 mg, 6.85 mmol) to provide the title electrophile as a colorless oil (1.141 g, 65%). Characterization: R_f = 0.36 (5% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.17 (dd, J = 4.11, 3.22 Hz, 1H), 5.11 (tsept, ^3J = 7.18, ^4J = 1.51 Hz, 1H), 4.21−4.11 (m, 2H), 4.04 (ddd, J = 11.36, 8.38, 2.78 Hz, 1H), 3.68−3.62 (m, 1H), 2.09−1.92 (m, 2H), 1.80−1.74 (m, 2H), 1.74−1.71 (m, 1H), 1.70 (s, 3H), 1.67−1.53 (5H), 1.62 (s, 3H), 1.50−1.41 (m, 1H), 1.41−1.32 (m, 1H), 1.24−1.15 (m, 1H), 0.93 (d, J = 6.66 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 131.2, 124.7, 100.8, 73.7, 62.6, 37.2, 34.6, 29.6, 28.0, 25.7, 25.4, 25.2, 19.8, 19.5, 17.6.

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*2-((3-Phenylpropyl)peroxy)tetrahydro-2H-pyran (**16**).* By following the general procedure for monoperoxyacetal synthesis using trifluoromethanesulfonates as described above, 3-phenylpropyl trifluoromethanesulfonate (**10**, 1.610 g, 6.00 mmol) was reacted with THP hydroperoxide (**1**, 709.0 mg, 6.00 mmol) and potassium *tert*-butoxide (673.0 mg, 6.00 mmol) to provide the title electrophile as a colorless oil (1.166 g, 82%). Characterization: R_f = 0.32 (5% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34−7.29 (m, 2H), 7.25−7.20 (m, 3H), 5.19 (dd, J = 4.20, 3.21 Hz, 1H), 4.15 (t, J = 6.46 Hz, 2H), 4.05 (ddd, J = 11.34, 8.32, 3.04 Hz, 1H), 3.70−3.63 (m, 1H), 2.75 (t, J = 7.74 Hz, 2H), 2.01 (tt, J = 7.74, 6.45 Hz, 2H), 1.81−1.72 (2H), 1.69−1.55 (4H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 141.6, 128.5, 128.4, 125.9, 100.8, 74.5, 62.6, 32.2, 29.5, 28.0, 25.2, 19.8.

*2-(Octan-2-ylperoxy)tetrahydro-2H-pyran (**17**).* By following the general procedure for monoperoxyacetal synthesis using trifluoromethanesulfonates as described above, octan-2-yl trifluoromethanesulfonate (**11**, 2.451 g, 9.35 mmol) was reacted with THP hydroperoxide (**1**, 1.104 g, 9.35 mmol) and potassium *tert*-butoxide (1.070 g, 9.35 mmol) to provide the title electrophile as a colorless oil (1.302 g, 60%). 2-(Octan-2-ylperoxy)tetrahydro-2*H*-pyran was obtained as an inseparable mixture of diastereomers. Characterization: R_f = 0.33 (3% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.17−5.10 (m, 1H), 4.28−4.22 (tq, J = 6.03, 6.05 Hz, 0.35H), 4.22−4.16 (tq, J = 6.20, 6.16 Hz, 0.58H), 4.04 (ddd, J = 11.20, 8.22, 2.83 Hz, 1H), 3.68−3.61 (m, 1H), 1.83−1.72 (2H), 1.72−1.54 (5H), 1.48−1.27 (9H), 1.25 (dd, J = 6.04, 6.07 Hz, 3H), 0.91 (t, J = 6.79 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 101.2, 100.7, 80.5, 80.3, 62.6, 62.6, 34.4, 31.8, 29.4, 29.3, 28.0, 27.9, 25.4, 25.4, 25.2, 22.6, 19.9, 19.8, 18.8, 18.6, 14.1, 14.1.

General Procedure for Attempted Ketene Acetal Synthesis via Transmetalation of Nonheterocyclic Nucleophiles (Scheme 1). A round-bottom flask with a magnetic stir bar was flame-dried, placed under vacuum, and cooled to 0 °C. Once chilled, the flask was charged with anhydrous THF (200−500 μL), evacuated once more, and flushed with N_2. To the system, the tributylstannyl substrate (2.00−3.00 equiv, 0.200−1.200 mmol) was added, resulting in a faint yellow solution. After several minutes, under the protection of nitrogen, *n*-BuLi was injected (1.80−2.00 equiv, 0.100−1.10 mmol, 11.0 M in hexanes), yielding a vibrant, neon-yellow-colored mixture. The reagents were stirred at 0 °C for 10 min, whereupon monoperoxyacetal (1.00 equiv, 100.0−400.0 μmol) in THF (200 μL) was introduced to the reaction dropwise. The solution was stirred for 5 min at 0 °C (during which time, the yellow color of the mixture faded away) before being warmed to room temperature. Upon warming, the system became dull gold; the crude solution's appearance did not change throughout the duration of the reaction period. Starting material disappearance was monitored with TLC; if the monoperoxyacetal was consumed (i.e., absence from TLC), one of the following workup methods were employed:

(1) No aqueous treatment. Materials were diluted with hexanes (approx. 3 mL) and promptly concentrated *in vacuo* at 30 °C. Following evaporation, crude oils were analyzed using NMR spectroscopy and, in some cases, purified via flash column chromatography (10−20% EtOAc/Hex) on deactivated silica (0.5% triethylamine additive) or neutral alumina.

(2) Aqueous treatment. Materials were diluted with saturated, aqueous potassium carbonate (3−5 mL), extracted with ether (3 × 15 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* at 30 °C. Following evaporation, crude oils were analyzed using NMR spectroscopy and, in some cases, purified via flash column chromatography (10−20% EtOAc/Hex) on deactivated silica (0.5% triethylamine additive) or neutral alumina.

In cases of no reaction, one of the workup schemes described above was employed after extended periods of stirring. Reactions of **3** or **15** were found to be unsuccessful, returning only the starting material or products of peroxide decomposition (NMR). Reaction of **5** was successful, as described below.

*(E/Z)-2-Dodecenyl Acetate (**18**).* Following the general procedure for transmetalation between tributylstannyl substrates and *n*-BuLi (with aqueous treatment) as detailed above, tributyl(1-ethoxyvinyl)-stannane (3.00 equiv, 392.0 mg, 1.05 mmol) was reacted with *n*-BuLi (2.80 equiv, 89.4 μL, 984.0 μmol, 11.0 M in hexanes) and (*E*/*Z*)-2-(dodec-2-en-1-ylperoxy) tetrahydro-2*H*-pyran (**5**, 1.00 equiv, 100.0 mg, 352.0 μmol) to provide a ketene acetal that, when mixed with water during workup, furnished the unsaturated ester, **18**, as a colorless oil (42.6 mg, 50%). This molecule was isolated via flash column chromatography (3% EtOAc/Hex) on deactivated silica (0.5% triethylamine additive). Characterization: R_f = 0.48 (5% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.74−5.67 (dtt, ^3J = 6.79, ^3J = 13.61, ^4J = 1.14 Hz, 1H), 5.53−5.46 (dtt, ^3J = 6.79, ^3J = 13.21, ^4J = 1.51 Hz, 1H), 4.44 (ddt, ^3J = 6.43, ^4J = 1.88, ^5J = 1.12 Hz, 2H), 2.01−1.95 (m, 2H), 1.99 (s, 3H), 1.35−1.27 (2H), 1.26−1.11 (14H), 0.81 (t, J = 7.19 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 170.9, 136.8, 123.6, 65.4, 32.3, 31.9, 29.6, 29.5, 29.3, 29.2, 28.9, 22.7, 21.1, 14.1. Spectral data were nearly identical to a previous report.[51]

General Procedure for Ketene *O*,*O*-Acetal Synthesis via α-Benzofuranyl Carbanions and Monoperoxyacetals. A round-bottom flask with a magnetic stir bar was flame-dried, placed under vacuum, and cooled to −78 °C. Upon chilling, the system was charged with anhydrous THF (2−5 mL), evacuated once more, and flushed with N_2. To the flask, benzofuran (2.00 equiv, 2.00 mmol) was added, resulting in a light-yellow solution. Under the protection of nitrogen, *n*-BuLi (2.00 equiv, 2.00 mmol, 11.0 M in hexanes) was introduced to the reaction, producing a vibrant, neon-yellow color, which intensified with every drop to an intense, burning orange. The mixture was stirred vigorously for 3 h at −78 °C, during which time, the reagents became a thick, pale-yellow suspension. After the allotted time, monoperoxyacetal (1.00 equiv, 1.00 mmol) was injected dropwise (neat). Following the addition of the electrophile, the system was warmed to room temperature; upon warming, the reactants became a bright, neon-yellow/orange solution. The reaction was allowed to proceed overnight at room temperature (during which reactant materials became dark amber orange) before an aliquot was abstracted for crude analysis (performed where noted, with the procedure outlined in general experimental guidelines). Following yield determination, the solution was diluted with hexanes (5 mL) and concentrated *in vacuo* (at room temperature). The crude material was purified via flash column chromatography (5% DCM/hexanes) on deactivated silica (0.5% triethylamine) to furnish an isolable ketene *O*,*O*-acetal in moderate yield. Ketene acetals, although isolable, decomposed significantly throughout the workup/purification process, as evidenced by TLC and NMR analysis.

*2-(Dodecyloxy)benzofuran (**19a**).* Using the general procedure for ketene *O*,*O*-acetal synthesis via intermolecular etherification as described above, benzofuran (2.00 equiv, 238.7 mg, 2.00 mmol) was reacted with *n*-BuLi (2.00 equiv, 181.8 μL, 2.00 mmol, 11.0 M in hexanes) and 2-(dodecylperoxy)tetrahydro-2*H*-pyran (**12**, 1.00 equiv, 286.5 mg, 1.00 mmol) to furnish the title ketene *O*,*O*-acetal as a white solid (231 mg, 76% crude; 118 mg, 39% isolated). This molecule decomposed significantly throughout the workup/purification process, as evidenced by TLC and NMR analysis. Characterization: R_f = 0.50 (5% DCM/Hex); ^{1}H NMR (600 MHz, C_6D_6): δ 7.34−7.31 (m, 1H), 7.26−7.23 (m, 1H), 7.13−7.09 (m, 1H), 7.01−6.97 (m, 1H), 5.25 (d, ^4J = 0.76 Hz, 1H), 3.71 (t, J = 6.42 Hz, 2H), 1.54−1.47 (2H), 1.37−1.12 (18H), 0.92 (t, J = 7.19 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, C_6D_6): δ 164.0, 149.4, 130.2, 123.2, 121.8, 119.2, 110.4, 76.7, 71.0, 32.2, 30.0, 29.9, 29.8, 29.7, 29.5, 29.0, 25.9, 23.0, 14.2. HRMS (FT-ICR, ESI$^+$): calcd for $C_{20}H_{30}NaO_2$ (M + Na), 325.2144; found, 325.2154.

*2-(Decyloxy)benzofuran (**19b**).* Using the general procedure for ketene *O*,*O*-acetal synthesis via intermolecular etherification as described above, benzofuran (2.00 equiv, 238.7 mg, 2.00 mmol) was reacted with *n*-BuLi (2.00 equiv, 181.8 μL, 2.00 mmol, 11.0 M in hexanes) and 2-(decylperoxy)tetrahydro-2*H*-pyran (**13a**, 1.00 equiv, 258.4 mg, 1.00 mmol) to furnish the title ketene *O*,*O*-acetal as a colorless oil at room temperature/white solid at low temperature (204

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mg, 75% crude; 149 mg, 54% isolated). This molecule decomposed significantly throughout the workup/purification process, as evidenced by TLC and NMR analysis. Characterization: R_f = 0.50 (5% DCM/Hex); ^{1}H NMR (600 MHz, C_6D_6): δ 7.35−7.30 (m, 1H), 7.27−7.22 (m, 1H), 7.14−7.08 (m, 1H), 7.01−6.96 (m, 1H), 5.25 (d, ^4J = 0.76 Hz, 1H), 3.71 (t, J = 6.43 Hz, 2H), 1.54−1.47 (2H), 1.43−1.10 (14H), 0.92 (t, J = 7.17 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, C_6D_6): δ 164.0, 149.4, 130.2, 123.2, 121.8, 119.2, 110.4, 76.7, 71.0, 32.2, 29.8, 29.8, 29.6, 29.5, 29.0, 25.9, 23.0, 14.2. HRMS (FT-ICR, ESI+): calcd for $C_{18}H_{26}NaO_2$ (M + Na), 297.1831; found, 297.1827.

*2-(Octyloxy)benzofuran (**19c**).* Using the general procedure for ketene *O,O*-acetal synthesis via intermolecular etherification as described above, benzofuran (2.00 equiv, 238.7 mg, 2.00 mmol) was reacted with *n*-BuLi (2.00 equiv, 181.8 μL, 2.00 mmol, 11.0 M in hexanes) and 2-(octylperoxy)tetrahydro-2*H*-pyran (**14a**, 1.00 equiv, 238.7 mg, 1.00 mmol) to furnish the title ketene *O,O*-acetal as a colorless oil (192 mg, 78% crude; 114 mg, 46% isolated). This molecule decomposed significantly throughout the workup/purification process, as evidenced by TLC and NMR analysis. Characterization: R_f = 0.50 (5% DCM/Hex); ^{1}H NMR (600 MHz, C_6D_6): δ 7.35−7.31 (m, 1H), 7.27−7.23 (m, 1H), 7.14−7.10 (m, 1H), 7.01−6.96 (m, 1H), 5.26 (d, ^4J = 0.76 Hz, 1H), 3.69 (t, J = 6.45 Hz, 2H), 1.52−1.45 (2H), 1.31−1.23 (2H), 1.23−1.09 (8H), 0.90 (t, J = 7.17 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, C_6D_6): δ 164.0, 149.5, 130.2, 123.2, 121.9, 119.2, 110.4, 76.7, 71.0, 32.0, 29.4, 29.4, 28.9, 25.9, 22.9, 14.2. HRMS (FT-ICR, ESI$^+$): calcd for $C_{16}H_{22}NaO_2$ (M + Na), 269.1518; found, 269.1522.

*2-((3,7-Dimethyloct-6-en-1-yl)oxy)benzofuran (**19d**).* Using the general procedure for ketene *O,O*-acetal synthesis via intermolecular etherification as described above, benzofuran (2.00 equiv, 238.7 mg, 2.00 mmol) was reacted with *n*-BuLi (2.00 equiv, 181.8 μL, 2.00 mmol, 11.0 M in hexanes) and 2-((3,7-dimethyloct-6-en-1-yl)peroxy) tetrahydro-2*H*-pyran (**15**, 1.00 equiv, 256.4 mg, 1.00 mmol) to furnish the title ketene *O,O*-acetal as a colorless oil (227 mg, 83% crude; 93.6 mg, 34% isolated). This molecule decomposed significantly throughout the workup/purification process, as evidenced by TLC and NMR analysis. Characterization: R_f = 0.34 (5% DCM/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45−7.40 (m, 1H), 7.39−7.34 (m, 1H), 7.24−7.19 (m, 1H), 7.19−7.13 (m, 1H), 5.56 (d, ^4J = 0.76 Hz, 1H), 5.18 (tsept, ^3J = 7.19, ^4J = 1.52 Hz, 1H), 4.29−4.20 (m, 2H), 2.17−2.01 (m, 2H), 2.00−1.92 (m, 1H), 1.85−1.74 (m, 1H), 1.76 (s, 3H), 1.74−1.64 (m, 1H), 1.68 (s, 3H), 1.51−1.43 (m, 1H), 1.36−1.27 (m, 1H), 1.04 (d, J = 6.66 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 163.5, 148.9, 131.5, 129.8, 124.6, 122.9, 121.5, 119.0, 110.2, 76.4, 69.6, 37.1, 35.8, 29.3, 25.8, 25.5, 19.4, 17.7. HRMS (FT-ICR, ESI$^+$): calcd for $C_{18}H_{24}NaO_2$ (M + Na), 295.1674; found, 295.1681.

*2-(3-Phenylpropoxy)benzofuran (**19e**).* Using the general procedure for ketene *O,O*-acetal synthesis via intermolecular etherification as described above, benzofuran (2.00 equiv, 238.7 mg, 2.00 mmol) was reacted with *n*-BuLi (2.00 equiv, 181.8 μL, 2.00 mmol, 11.0 M in hexanes) and 2-((3-phenylpropyl)peroxy)tetrahydro-2*H*-pyran (**16**, 1.00 equiv, 236.3 mg, 1.00 mmol) to furnish the title ketene *O,O*-acetal as a colorless oil at room temperature/white solid at low temperature (203 mg, 81% crude; 88.2 mg, 35% isolated). This molecule decomposed significantly throughout the workup/purification process, as evidenced by TLC and NMR analysis. Characterization: R_f = 0.20 (5% DCM/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29−7.24 (m, 1H), 7.24−7.16 (m, 3H), 7.15−7.09 (m, 3H), 7.08−7.04 (m, 1H), 7.04−7.00 (m, 1H), 5.38 (d, ^4J = 0.76 Hz, 1H), 4.04 (t, J = 6.42 Hz, 2H), 2.74 (t, J = 7.56 Hz, 2H), 2.09−2.03 (tt, J = 7.57, 6.42 Hz, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 163.4, 148.9, 141.0, 129.7, 128.6, 126.2, 123.0, 121.6, 119.1, 110.2, 76.6, 70.1, 31.9, 30.5. HRMS (FT-ICR, ESI$^+$): calcd for $C_{17}H_{16}NaO_2$ (M + Na), 275.1048; found, 275.1046.

General Procedure for Acid-Catalyzed Hydration of Ketene *O,O*-Acetals. A scintillation vial with a magnetic stir bar was charged with an aliquot of pure ketene *O,O*-acetal (25.0−50.0 mg) and THF (3−5 mL). The vial was capped with a septum, flushed with nitrogen, and allowed to stir for several minutes. To the system, water (5 mL) and 10% aq sulfuric acid (300 μL) were injected sequentially, resulting in a homogeneous, clear solution. The reagents were left to mix overnight at room temperature before being diluted with saturated, aq potassium carbonate (3 mL), extracted with EtOAc (copious amounts used, 3×), dried with sodium sulfate, filtered, and concentrated *in vacuo* (at room temperature). The obtained, yellow residue was purified via flash column chromatography (8% EtOAc/Hex) to furnish esters, derived from initial hemi-orthoester formation, in high yield.

*Octyl 2-(2-Hydroxyphenyl)acetate (**20a**).* By following the general procedure for acid-catalyzed hydration of ketene acetals as described above, 2-(octyloxy)benzofuran (**19c**, 50.6 mg, 205.0 μmol) was reacted with water (5 mL) and 10% aq sulfuric acid (300 μL) to provide the title ester as a colorless oil (47.1 mg, 87%). Characterization: R_f = 0.43 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.85−7.47 (broad s, 1H), 7.25−7.18 (m, 1H), 7.16−7.11 (m, 1H), 6.99−6.94 (m, 1H), 6.94−6.88 (m, 1H), 4.17 (t, J = 6.80 Hz, 2H), 3.71 (s, 2H), 1.72−1.64 (m, 2H), 1.43−1.21 (10H), 0.93 (t, J = 7.17 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 174.1, 155.3, 131.0, 129.2, 120.8, 120.7, 117.6, 66.1, 38.0, 31.8, 29.2, 28.4, 25.8, 22.7, 14.1. HRMS (FT-ICR, ESI$^+$): calcd for $C_{16}H_{24}NaO_3$ (M + Na), 287.1623; found, 287.1620.

*3,7-Dimethyloct-6-enyl 2-(2-Hydroxyphenyl)acetate (**20b**).* By following the general procedure for acid-catalyzed hydration of ketene acetals as described above, 2-((3,7-dimethyloct-6-en-1-yl)oxy)-benzofuran (**19d**, 27.6 mg, 101.0 μmol) was reacted with water (5 mL) and 10% aq sulfuric acid (300 μL) to provide the title ester as a colorless oil (24.7 mg, 84%). Characterization: R_f = 0.42 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.74−7.51 (broad s, 1H), 7.26−7.19 (m, 1H), 7.16−7.09 (m, 1H), 7.01−6.95 (m, 1H), 6.94−6.87 (m, 1H), 5.11 (tsept, ^3J = 7.18, ^4J = 1.51 Hz, 1H), 4.27−4.15 (m, 2H), 3.70 (s, 2H), 2.07−1.92 (m, 2H), 1.77−1.68 (m, 1H), 1.72 (d, ^4J = 1.14 Hz, 3H), 1.63 (d, ^4J = 1.14 Hz, 3H), 1.60−1.53 (m, 1H), 1.53−1.46 (m, 1H), 1.40−1.32 (m, 1H), 1.25−1.16 (m, 1H), 0.93 (d, J = 6.79 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 174.1, 155.3, 131.5, 131.0, 129.2, 124.5, 120.9, 120.7, 117.8, 64.5, 38.1, 36.9, 35.2, 29.4, 25.7, 25.4, 19.4, 17.7. HRMS (FT-ICR, ESI$^+$): calcd for $C_{18}H_{26}NaO_3$ (M + Na), 313.1780; found, 313.1777.

*3-Phenylpropyl 2-(2-Hydroxyphenyl) Acetate (**20c**).* By following the general procedure for acid-catalyzed hydration of ketene acetals as described above, 2-(3-phenylpropoxy)benzofuran (**19e**, 31.1 mg, 123.0 μmol) was reacted with water (5 mL) and 10% aq sulfuric acid (300 μL) to provide the title ester as a colorless oil (27.5 mg, 83%). Characterization: R_f = 0.34 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.79−7.36 (broad s, 1H), 7.36−7.30 (m, 2H), 7.28−7.22 (m, 2H), 7.22−7.13 (m, 3H), 7.01−6.96 (m, 1H), 6.96−6.90 (m, 1H), 4.20 (t, J = 6.44 Hz, 2H), 3.72 (s, 2H), 2.71 (t, J = 7.53 Hz, 2H), 2.06−1.99 (tt, J = 7.53, 6.43 Hz, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 173.9, 155.2, 140.9, 131.0, 129.2, 128.5, 128.4, 126.1, 120.9, 120.7, 117.6, 65.2, 37.9, 32.0, 30.0. HRMS (FT-ICR, ESI$^+$): calcd for $C_{17}H_{18}NaO_3$ (M + Na), 293.115; found, 293.1158.

General Procedure for Ketene *N,O*-Acetal Synthesis via α-Lithiated Indoles and Electrophilic Peroxides.[29a] A round-bottom flask with a magnetic stir bar was flame-dried, capped with a septum, and placed under vacuum. After several minutes, the system was charged with anhydrous THF (4 mL), evacuated once more, and flushed with N_2. To the flask, 1-methylindole (2.00 equiv, 2.00 mmol) was added, resulting in a faint-gold solution. The flask was cooled to −78 °C, whereupon *n*-BuLi (2.00 equiv, 2.00 mmol, 11.0 M in hexanes) was introduced to the reaction, producing a vibrant, neon-yellow color, which intensified with every drop to a dark, burning orange. After five minutes, the mixture was removed from its cold bath and was allowed to warm to room temperature. The solution was stirred vigorously for 3 h, during which time, the reagents became a thick, peach-colored suspension. After the allotted time, the system was cooled back to −78 °C and monoperoxyacetal (1.00 equiv, 1.00 mmol) was injected (neat), producing a reaction mixture color change (colors: peach to yellow to lime green; at this time, the flask is still at −78 °C and the described changes are occurring with every additional drop of peroxide). Following the addition of the electrophile, the

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system was warmed to room temperature; upon warming, the reactants became a dull tan/gold solution. The reaction was allowed to proceed for 45 min before an aliquot was abstracted for crude analysis (performed where noted, with the procedure outlined in general experimental guidelines). Following yield determination, the solution was transferred to a scintillation vial and concentrated *in vacuo* (at room temperature). The crude material was purified via flash column chromatography (3% EtOAc/Hex) on deactivated silica (0.5% triethylamine) to provide an isolable ketene *N*,*O*-acetal in satisfactory yield. Ketene acetals, although isolable, decomposed throughout the workup/purification process, as evidenced by TLC and NMR analysis.

*2-Decyloxy-1-methylindole (**21a**).* Using the general procedure for ketene *N*,*O*-acetal synthesis via intermolecular etherification as described above, 1-methylindole (2.00 equiv, 271. mg, 2.00 mmol) was reacted with *n*-BuLi (2.00 equiv, 181.8 μL, 2.00 mmol, 11.0 M in hexanes) and 2-(decylperoxy)tetrahydro-2*H*-pyran (**13a**, 1.00 equiv, 258.0 mg, 1.00 mmol) to furnish the title ketene *N*,*O*-acetal as a lime-green oil (216 mg, 75%). The same molecule (**21a**) was produced following an incomplete reaction between 1-methylindole (2.00 equiv, 271.0 mg, 2.00 mmol), *n*-BuLi (2.00 equiv, 181.8 μL, 2.00 mmol, 11.0 M), and 1-(*tert*-butylperoxy)decane (**13b**, 1.00 equiv, 230.4 mg, 1.00 mmol) (90.4 mg, 31% by qNMR; 48% of **13b** unreacted by qNMR). This molecule decomposed throughout the workup/purification process, as evidenced by TLC and NMR analysis. Characterization: R_f = 0.42 (3% EtOAc/Hex); ^{1}H NMR (600 MHz, C_6D_6): δ 7.68−7.62 (m, 1H), 7.29−7.24 (m, 1H), 7.23−7.18 (m, 1H), 7.01−6.95 (m, 1H), 5.53 (d, ^4J = 0.76 Hz, 1H), 3.79 (t, J = 6.42 Hz, 2H), 3.10 (s, 3H), 1.62−1.55 (2H), 1.41−1.16 (14H), 0.94 (t, J = 7.18 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, C_6D_6): δ 153.4, 133.3, 120.0, 119.5, 119.1, 108.2, 76.4, 70.4, 32.2, 29.9, 29.7, 29.6, 29.2, 27.0, 26.2, 23.0, 14.3. HRMS (FT-ICR, ESI$^+$): calcd for $C_{19}H_{29}NNaO$ (M + Na), 310.2147; found, 310.2147.

*2-Octyloxy-1-methylindole (**21b**).* Using the general procedure for ketene *N*,*O*-acetal synthesis via intermolecular etherification as described above, 1-methylindole (2.00 equiv, 176. mg, 1.30 mmol) was reacted with *n*-BuLi (2.00 equiv, 181.8 μL, 2.00 mmol, 11.0 M in hexanes) and 2-(octylperoxy)tetrahydro-2*H*-pyran (**14a**, 1.00 equiv, 150.0 mg, 651.0 μmol) to furnish the title ketene *N*,*O*-acetal as a lime-green oil (120 mg, 71%). This molecule decomposed throughout the workup/purification process, as evidenced by TLC and NMR analysis. Characterization: R_f = 0.50 (3% EtOAc/Hex); ^{1}H NMR (600 MHz, C_6D_6): δ 7.67−7.63 (m, 1H), 7.29−7.24 (m, 1H), 7.24−7.19 (m, 1H), 7.01−6.97 (m, 1H), 5.53 (d, ^4J = 0.76 Hz, 1H), 3.78 (t, J = 6.43 Hz, 2H), 3.10 (s, 3H), 1.61−1.54 (2H), 1.34−1.17 (10H), 0.93 (t, J = 7.17 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, C_6D_6): δ 153.4, 133.3, 120.0, 119.5, 119.1, 108.2, 76.5, 70.4, 32.1, 29.5, 29.5, 29.2, 27.0, 26.2, 22.9, 14.2. HRMS (FT-ICR, ESI$^+$): calcd for $C_{17}H_{25}NNaO$ (M + Na), 282.1834; found, 282.1833.

*2-((3,7-Dimethyl-6-en-1-yl)oxy)-1-methylindole (**21c**).* Using the general procedure for ketene *N*,*O*-acetal synthesis via intermolecular etherification as described above, 1-methylindole (2.00 equiv, 94.9 mg, 702.0 μmol) was reacted with *n*-BuLi (2.00 equiv, 63.8 μL, 702.0 μmol, 11.0 M in hexanes) and 2-((3,7-dimethyloct-6-en-1-yl)peroxy) tetrahydro-2*H*-pyran (**15**, 1.00 equiv, 90.0 mg, 351.0 μmol) to furnish the title ketene *N*,*O*-acetal as a lime-green oil (72.6 mg, 73%). This molecule decomposed slightly upon workup and purification, as detected via TLC/NMR analysis. Characterization: R_f = 0.50 (3% EtOAc/Hex); ^{1}H NMR (600 MHz, C_6D_6): δ 7.67−7.63 (m, 1H), 7.29−7.25 (m, 1H), 7.24−7.19 (m, 1H), 7.01−6.97 (m, 1H), 5.53 (d, ^4J = 0.76 Hz, 1H), 5.18 (tsept, ^3J = 7.18, ^4J = 1.52 Hz, 1H), 3.90−3.81 (m, 2H), 3.10 (s, 3H), 2.09−1.96 (m, 2H), 1.72−1.64 (m, 1H), 1.69 (s, 3H), 1.63−1.52 (m, 1H), 1.57 (s, 3H), 1.44−1.38 (m, 1H), 1.38−1.32 (m, 1H), 1.21−1.13 (m, 1H), 0.84 (d, J = 6.80 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, C_6D_6): δ 153.4, 133.3, 131.1, 125.0, 120.0, 119.5, 119.1, 108.2, 76.5, 68.7, 37.3, 36.0, 29.6, 27.0, 25.8, 25.7, 19.5, 17.6. HRMS (FT-ICR, ESI$^+$): calcd for $C_{19}H_{27}NNaO$ (M + Na), 308.1990; found, 308.1988.

*2-(Octan-2-yloxy)-1-methylindole (**22**).* Using the general procedure for ketene *N*,*O*-acetal synthesis via intermolecular etherification as described above, 1-methylindole (2.00 equiv, 271.0 mg, 2.00 mmol) was reacted with *n*-BuLi (2.00 equiv, 181.8 μL, 2.00 mmol, 11.0 M in hex.) and 2-(octan-2-ylperoxy)tetrahydro-2H-pyran (**17**, 1.00 equiv, 230.4 mg, 1.00 mmol) to furnish the title ketene *N*,*O*-acetal as a lime-green oil (90.9 mg, 35%). This molecule decomposed throughout the workup/purification process, as evidenced by TLC and NMR analysis. Characterization: R_f = 0.58 (3% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36−7.30 (m, 1H), 7.07−7.02 (m, 1H), 7.00−6.92 (m, 2H), 5.44 (s, 1H), 4.34−4.23 (1H), 3.46 (s, 3H), 1.79−1.69 (m, 1H), 1.59−1.51 (m, 1H), 1.44−1.34 (m, 1H), 1.34−1.28 (m, 1H), 1.30 (d, J = 6.25 Hz, 3H), 1.28−1.10 (6H), 0.81 (t, J = 7.18 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 152.8, 132.6, 127.5, 119.5, 118.9, 118.4, 107.9, 77.7, 76.5, 36.4, 31.8, 29.3, 27.6, 25.5, 22.7, 19.8, 14.1. HRMS (FT-ICR, ESI$^+$): calcd for $C_{17}H_{25}NNaO$ (M + Na), 282.1834; found, 282.1829.

*2-(Decyloxy)-4-methoxy-1-methylindole (**23a**).* Using the general procedure for ketene *N*,*O*-acetal synthesis via intermolecular etherification as described above, 4-methoxy-1-methylindole (2.00 equiv, 98.7 mg, 600.0 μmol) was reacted with *n*-BuLi (2.00 equiv, 54.6 μL, 600.0 μmol, 11.0 M in hex.) and 2-(decylperoxy)tetrahydro-2*H*-pyran (**13a**, 1.00 equiv, 77.5 mg, 300.0 μmol) to furnish the title ketene *N*,*O*-acetal as a lime-green oil (67.9 mg, 71%). This molecule decomposed throughout the workup/purification process, as evidenced by TLC and NMR analysis. Characterization: R_f = 0.37 (3% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.92 (t, J = 7.95 Hz, 1H), 6.73 (d, J = 7.93 Hz, 1H), 6.45 (d, J = 7.94 Hz, 1H), 5.55 (s, 1H), 4.02 (t, J = 6.58 Hz, 2H), 3.85 (s, 3H), 3.46 (s, 3H), 1.78−1.71 (2H), 1.42−1.34 (2H), 1.31−1.11 (12H), 0.93 (t, J = 7.19 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 152.4, 151.9, 133.9, 119.7, 117.0, 101.9, 100.2, 73.0, 70.7, 55.4, 32.0, 29.6, 29.4, 29.1, 27.8, 26.0, 22.7, 14.2. HRMS (FT-ICR, ESI$^+$): calcd for $C_{20}H_{31}NNaO_2$ (M + Na), 340.2253; found, 340.2250.

*2-(Octyloxy)-4-methoxy-1-methylindole (**23b**).* Using the general procedure for ketene *N*,*O*-acetal synthesis via intermolecular etherification as described above, 4-methoxy-1-methylindole (2.00 equiv, 98.7 mg, 600.0 μmol) was reacted with *n*-BuLi (2.00 equiv, 54.6 μL, 600.0 μmol, 11.0 M in hex.) and 2-(octylperoxy)tetrahydro-2*H*-pyran (**14a**, 1.00 equiv, 69.1 mg, 300.0 μmol) to furnish the title ketene *N*,*O*-acetal as a lime-green oil (64.8 mg, 75%). This molecule decomposed throughout the workup/purification process, as evidenced by TLC and NMR analysis. Characterization: R_f = 0.38 (3% ETOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.93 (t, J = 7.97 Hz, 1H), 6.74 (d, J = 7.94 Hz, 1H), 6.46 (d, J = 7.96 Hz, 1H), 5.56 (s, 1H), 4.03 (t, J = 6.43 Hz, 2H), 3.86 (s, 3H), 3.46 (s, 3H), 1.79−1.72 (tt, J = 7.18, 6.80 Hz, 2H), 1.42−1.35 (tt, J = 7.67, 6.78 Hz, 2H), 1.32−1.10 (8H), 0.82 (t, J = 7.18 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 152.4, 151.9, 133.9, 119.7, 117.0, 101.9, 100.2, 73.0, 70.7, 55.4, 31.9, 29.3, 29.3, 29.0, 27.8, 26.0, 22.7, 14.1. HRMS (FT-ICR, ESI$^+$): calcd for $C_{18}H_{27}NNaO_2$ (M + Na), 312.1940; found, 312.1938.

*2-((3,7-Dimethyloct-6-enyl)oxy)-4-methoxy-1-methylindole (**23c**).* Using the general procedure for ketene *N*,*O*-acetal synthesis via intermolecular etherification as described above, 4-methoxy-1-methylindole (2.00 equiv, 98.7 mg, 600.0 μmol) was reacted with *n*-BuLi (2.00 equiv, 54.6 μL, 600.0 μmol, 11.0 M in hex.) and 2-((3,7-dimethyloct-6-en-1-yl)peroxy)tetrahydro-2*H*-pyran (**15**, 1.00 equiv, 76.9 mg, 300.0 μmol) to furnish the title ketene *N*,*O*-acetal as a lime-green oil (57.2 mg, 78%). This molecule decomposed throughout the workup/purification process, as evidenced by TLC and NMR analysis. Characterization: R_f = 0.60 (3% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.93 (t, J = 7.98 Hz, 1H), 6.74 (d, J = 8.01 Hz, 1H), 6.46 (d, J = 7.94 Hz, 1H), 5.57 (s, 1H), 5.03 (tsept, ^3J = 7.18, ^4J = 1.50 Hz, 1H), 4.12−4.04 (m, 2H), 3.86 (s, 3H), 3.46 (s, 3H), 2.02−1.86 (m, 2H), 1.85−1.78 (m, 1H), 1.68−1.55 (m, 2H), 1.61 (s, 3H), 1.54 (s, 3H), 1.37−1.29 (m, 1H), 1.22−1.12 (m, 1H), 0.89 (d, J = 6.43 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 152.4, 151.9, 133.9, 131.4, 124.6, 119.7, 117.0, 101.9, 100.2, 73.0, 69.0, 55.4, 37.1, 35.8, 29.6, 27.8, 25.8, 25.5, 19.6, 17.7. HRMS (FT-ICR, ESI$^+$): calcd for $C_{20}H_{29}NNaO_2$ (M + Na), 338.2096; found, 338.2092.

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*7-Butyl-6-nitro-1-methylindole (**24**).* Using the general procedure for ketene *N,O*-acetal synthesis via intermolecular etherification as described above, 6-nitro-1-methylindole (2.00 equiv, 176.2 mg, 1.00 mmol) was reacted with *n*-BuLi (2.00 equiv, 90.9 μL, 1.00 mmol, 11.0 M in hex.) and 2-(decylperoxy)tetrahydro-2*H*-pyran (**13a**, 1.00 equiv, 129.2 mg, 500. μmol) to provide no ketene *N,O*-acetal but, rather, 7-butyl-6-nitro-1-methylindole as a dark-brown oil, following isolation (35.9 mg, 31%). This product, formed by undesired nucleophilic aromatic substitution of *n*-BuLi, matched the predictions laid forth by previous groups.[31] Characterization: R_f = 0.32 (5% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8.69 Hz, 1H), 7.48 (d, *J* = 8.69 Hz, 1H), 7.19 (d, *J* = 3.02 Hz, 1H), 6.53 (d, *J* = 3.02 Hz, 1H), 4.11 (s, 3H), 3.23 (t, *J* = 8.30 Hz, 2H), 1.85−1.77 (tt, *J* = 7.54, 7.54 Hz, 2H), 1.59−1.51 (tq, *J* = 7.54, 7.55 Hz, 2H), 1.02 (t, *J* = 7.55 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 145.6, 135.8, 133.8, 133.0, 123.1, 118.9, 116.6, 101.8, 37.5, 34.6, 26.9, 22.9, 13.9. HRMS (FT-ICR, ESI$^+$): calcd for $C_{13}H_{16}N_2NaO_2$ (M + Na), 255.1110; found, 255.1104.

General Procedure for Ketene *N,O*-Acetal Synthesis via Pyridine-Based Nucleophiles and Peroxides.[52−55] A round-bottom flask with a magnetic stir bar was flame-dried, subjected to reduced pressure, and cooled to −78 °C. Upon chilling, the system was charged with anhydrous THF (2−5 mL), placed under vacuum once more, and flushed with N_2. To the flask, a 2-bromopyridine derivative (2.00 equiv, usually 2.00 mmol) was added, resulting in a colorless solution. Under the protection of nitrogen, *n*-BuLi (2.00 equiv, usually 2.00 mmol, 11.0 M in hexanes) was introduced to the reaction, producing an intense, neon-yellow color, which intensified with every drop to a dark orange/scarlet-colored mixture. The reagents were stirred vigorously for 1 h at −78 °C, whereupon monoperoxyacetal (1.00 equiv, usually 1.00 mmol) was injected into the flask, neat and dropwise. Throughout the addition of the electrophile, a slight, evergreen color was elicited from the reaction solution; the reactants darkened to a black color within moments of stirring at low temperature. For 5 min, the reactants were mixed at −78 °C before the flask was removed from the cooling bath and allowed to warm to room temperature. After approximately 30 min, complete disappearance of the starting material was observed, and the crude solution was transferred to a scintillation vial for evaporation *in vacuo* (at room temperature). The crude material was purified via flash column chromatography (1−3% EtOAc/Hex) on deactivated silica (0.5% triethylamine additive) to furnish an isolable ketene *N,O*-acetal in good to excellent yield.

*2-(Decyloxy)pyridine (**25a**).* By following the general procedure for ketene *N,O*-acetal synthesis via pyridine-based nucleophiles and electrophilic peroxides, as described above, 2-bromopyridine (2.00 equiv, 319.2 mg, 2.00 mmol) was reacted with *n*-BuLi (2.00 equiv, 181.8 μL, 2.00 mmol, 11.0 M in hex.) and 2-(decylperoxy)tetrahydro-2*H*-pyran (**13a**, 1.00 equiv, 258.4 mg, 1.00 mmol) to furnish the title molecule as a colorless oil (186.1 mg, 79%). Characterization: R_f = 0.32 (3% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08 (ddd, ^5J = 0.76, ^4J = 1.90, ^3J = 4.92 Hz, 1H), 7.48 (ddd, ^4J = 1.88, ^3J = 7.15, ^3J = 8.17 Hz, 1H), 6.77 (ddd, ^4J = 0.76, ^3J = 4.93, ^3J = 7.17 Hz, 1H), 6.65 (dt, ^3J = 8.33, ^5J = 0.76 Hz, 1H), 4.20 (t, *J* = 6.79 Hz, 2H), 1.73−1.67 (tt, *J* = 7.19, 6.78 Hz, 2H), 1.40−1.34 (2H), 1.31−1.14 (12H), 0.81 (t, *J* = 7.19 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 164.0, 146.8, 138.6, 116.4, 111.1, 66.1, 31.9, 29.6, 29.6, 29.4, 29.3, 29.1, 26.1, 22.7, 14.1. HRMS (FT-ICR, ESI$^+$): calcd for $C_{15}H_{25}NNaO$ (M + Na), 258.1834; found, 258.1829.

*2-(3-Phenylpropoxy)pyridine (**25b**).* By following the general procedure for ketene *N,O*-acetal synthesis via pyridine-based nucleophiles and electrophilic peroxides, as described above, 2-bromopyridine (2.00 equiv, 319.2 mg, 2.00 mmol) was reacted with *n*-BuLi (2.00 equiv, 181.8 μL, 2.00 mmol, 11.0 M in hex.) and 2-((3-phenylpropyl)peroxy) tetrahydro-2*H*-pyran (**16**, 1.00 equiv, 236.3 mg, 1.00 mmol) to furnish the title molecule as a colorless oil (168.7 mg, 79%). Characterization: R_f = 0.26 (3% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18 (ddd, ^5J = 0.76, ^4J = 1.88, ^3J = 4.94 Hz, 1H), 7.62−7.58 (ddd, ^4J = 2.13, ^3J = 7.16, ^3J = 8.41 Hz, 1H), 7.34−7.30 (m, 2H), 7.28−7.24 (m, 2H), 7.24−7.20 (m, 1H), 6.89 (ddd, ^4J = 0.76, ^3J = 5.27, ^3J = 7.16 Hz, 1H), 6.78 (dt, ^3J = 8.30 Hz, ^5J = 0.76, 1H), 4.35 (t, *J* = 6.45 Hz, 2H), 2.83 (t, *J* = 7.94 Hz, 2H), 2.18−2.11 (tt, *J* = 7.91, 6.41 Hz, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 163.9, 146.8, 141.7, 138.6, 128.5, 128.4, 125.9, 116.6, 111.1, 65.2, 32.3, 30.7. HRMS (FT-ICR, ESI$^+$): calcd for $C_{14}H_{15}NNaO$ (M + Na), 236.1051; found, 236.1044.

*2-((3,7-Dimethyloct-6-enyl)oxy)pyridine (**25c**).* By following the general procedure for ketene *N,O*-acetal synthesis via pyridine-based nucleophiles and electrophilic peroxides, as described above, 2-bromopyridine (2.00 equiv, 319.2 mg, 2.00 mmol) was reacted with *n*-BuLi (2.00 equiv, 181.8 μL, 2.00 mmol, 11.0 M in hexanes) and 2-((3,7-dimethyloct-6-en-1-yl)peroxy)tetrahydro-2*H*-pyran (**15**, 1.00 equiv, 256.4 mg, 1.00 mmol) to furnish the title molecule as a colorless oil (217.1 mg, 93%). Characterization: R_f = 0.46 (3% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.07 (ddd, ^5J = 0.76, ^4J = 1.88, ^3J = 4.90 Hz, 1H), 7.49−7.45 (ddd, ^4J = 1.89, ^3J = 7.19, ^3J = 8.30 Hz, 1H), 6.76 (ddd, ^4J = 0.76, ^3J = 4.91, ^3J = 7.17 Hz, 1H), 6.64 (dt, ^3J = 8.33 Hz, ^5J = 0.76, 1H), 5.03 (tsept, ^3J = 7.18, ^4J = 1.51 Hz, 1H), 4.29−4.20 (m, 2H), 2.01−1.86 (m, 2H), 1.79−1.72 (m, 1H), 1.65−1.55 (m, 1H), 1.60 (d, ^4J = 1.11 Hz, 3H), 1.55−1.47 (m, 1H), 1.53 (s, 3H), 1.34−1.30 (m, 1H), 1.20−1.11 (m, 1H), 0.89 (d, *J* = 6.81 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): 164.0, 146.9, 138.5, 131.2, 124.8, 116.2, 111.1, 64.3, 37.2, 36.0, 29.6, 25.7, 25.5, 19.6, 17.7. HRMS (FT-ICR, ESI$^+$): calcd for $C_{15}H_{23}NNaO$ (M + Na), 256.1677; found, 256.1669.

*2-(Octan-2-yloxy)pyridine (**25d**).* By following the general procedure for ketene *N,O*-acetal synthesis via pyridine-based nucleophiles and electrophilic peroxides, as described above, 2-bromopyridine (2.00 equiv, 145.5 mg, 912. μmol) was reacted with *n*-BuLi (2.00 equiv, 83.0 μL, 912.0 μmol, 11.0 M in hexanes) and 2-(octan-2-ylperoxy)tetrahydro-2*H*-pyran (**17**, 1.00 equiv, 105.0 mg, 456.0 μmol) to furnish the title molecule as a colorless oil (38.2 mg, 40%). Characterization: R_f = 0.72 (5% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.09−8.02 (m, 1H), 7.49−7.42 (m, 1H), 6.79−6.70 (m, 1H), 6.64−6.57 (m, 1H), 5.14−5.07 (tq, *J* = 6.04, 6.07 Hz, 0.80H), 5.07−5.02 (m, 0.22H), 1.73−1.43 (m, 3H), 1.41−1.31 (m, 1H), 1.30−1.15 (6H), 1.27 (d, *J* = 6.06 Hz, 3H), 0.80 (t, *J* = 7.19 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 163.8, 146.8, 138.5, 116.1, 111.6, 71.4, 36.4, 31.8, 29.3, 25.5, 22.6, 19.9, 14.1. HRMS (FT-ICR, ESI$^+$): calcd for $C_{13}H_{21}NNaO$ (M + Na), 230.1521; found, 230.1513.

*2-(Decyloxy)-4-methylpyridine (**26a**).* By following the general procedure for ketene *N,O*-acetal synthesis via pyridine-based nucleophiles and electrophilic peroxides, as described above, 2-bromo-4-methylpyridine (2.00 equiv, 195.1 mg, 1.100 mmol) was reacted with *n*-BuLi (2.00 equiv, 100.0 μL, 1.100 mmol, 11.0 M in hexanes) and 2-(decylperoxy)tetrahydro-2*H*-pyran (**13a**, 1.00 equiv, 142.1 mg, 550.0 μmol) to furnish the title compound as a colorless oil (104.3 mg, 76%). Characterization: R_f = 0.39 (3% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): 7.93 (d, *J* = 5.29 Hz, 1H), 6.61 (d, *J* = 5.29 Hz, 1H), 6.48 (s, 1H), 4.18 (t, *J* = 6.80 Hz, 2H), 2.22 (s, 3H), 1.72−1.66 (tt, *J* = 7.17, 6.80 Hz, 2H), 1.40−1.32 (2H), 1.31−1.13 (12H), 0.81 (t, *J* = 7.18 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 164.4, 149.7, 146.3, 118.0, 111.1, 65.9, 31.9, 29.6, 29.6, 29.4, 29.3, 29.1, 26.1, 22.7, 20.8, 14.1. HRMS (FT-ICR, ESI$^+$): calcd for $C_{16}H_{27}NNaO$ (M + Na), 272.1990; found, 272.1982.

*2-(3-Phenylpropoxy)-4-methylpyridine (**26b**).* By following the general procedure for ketene *N,O*-acetal synthesis via pyridine-based nucleophiles and electrophilic peroxides, as described above, 2-bromo-4-methylpyridine (2.00 equiv, 195.1 mg, 1.100 mmol) was reacted with *n*-BuLi (2.00 equiv, 100.0 μL, 1.100 mmol, 11.0 M in hexanes) and 2-((3-phenylpropyl)peroxy)tetrahydro-2*H*-pyran (**16**, 1.00 equiv, 130.0 mg, 550.0 μmol) to furnish the title compound as a colorless oil (99.1 mg, 79%). Characterization: R_f = 0.28 (3% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): 7.91 (d, *J* = 5.27 Hz, 1H), 7.23−7.16 (m, 2H), 7.15−7.07 (m, 3H), 6.59 (dd, ^4J = 0.76, ^3J = 5.29 Hz, 1H), 6.47 (s, 1H), 4.21 (t, *J* = 6.45 Hz, 2H), 2.70 (t, *J* = 7.94 Hz, 2H), 2.20 (s, 3H), 2.04−1.97 (tt, *J* = 7.94, 6.44 Hz, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 164.3, 149.9, 149.8, 141.8, 128.5, 128.3, 125.9,

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118.2, 111.1, 65.1, 32.3, 30.8, 20.9. HRMS (FT-ICR, ESI$^+$): calcd for $C_{15}H_{17}NNaO$ (M + Na), 250.1208; found, 250.1198.

*2-((3,7-Dimethyloct-6-enyl)oxy)-4-methylpyridine (**26c**).* By following the general procedure for ketene *N,O*-acetal synthesis via pyridine-based nucleophiles and electrophilic peroxides, as described above, 2-bromo-4-methylpyridine (2.00 equiv, 195.1 mg, 1.100 mmol) was reacted with *n*-BuLi (2.00 equiv, 100.0 μL, 1.100 mmol, 11.0 M in hexanes) and 2-((3,7-dimethyloct-6-en-1-yl)peroxy)-tetrahydro-2*H*-pyran (**15**, 1.00 equiv, 141.0 mg, 550.0 μmol) to furnish the title molecule as a colorless oil (101.1 mg, 74%). Characterization: R_f = 0.29 (3% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.93 (d, *J* = 5.28 Hz, 1H), 6.60 (d, *J* = 5.29 Hz, 1H), 6.46 (s, 1H), 5.03 (tsept, ^3J = 7.17, ^4J = 1.52 Hz, 1H), 4.28−4.18 (m, 2H), 2.21 (s, 3H), 2.01−1.84 (m, 2H), 1.78−1.70 (m, 1H), 1.65−1.56 (m, 1H), 1.60 (d, ^4J = 1.52 Hz, 3H), 1.55−1.46 (m, 1H), 1.53 (s, 3H), 1.37−1.29 (m, 1H), 1.17−1.11 (m, 1H), 0.88 (d, *J* = 6.78 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 Hz, $CDCl_3$): δ 164.3, 149.9, 146.3, 131.2, 124.8, 118.1, 111.2, 64.4, 37.2, 36.0, 29.6, 25.7, 25.5, 20.9, 19.6, 17.7. HRMS (FT-ICR, ESI$^+$): calcd for $C_{16}H_{25}NNaO$ (M + Na), 270.1834; found, 270.1825.

*2-(Decyloxy)-6-methoxypyridine (**27a**).* By following the general procedure for ketene *N,O*-acetal synthesis via pyridine-based nucleophiles and electrophilic peroxides, as described above, 2-bromo-6-methoxypyridine (2.00 equiv, 387.7 mg, 2.00 mmol) was reacted with *n*-BuLi (2.00 equiv, 181.8 μL, 2.00 mmol, 11.0 M in hexanes) and 2-(decylperoxy) tetrahydro-2*H*-pyran (**13a**, 1.00 equiv, 258.4 mg, 1.00 mmol) to furnish the title molecule as a colorless oil (238.7 mg, 90%). Characterization: R_f = 0.42 (2% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39 (t, *J* = 7.92 Hz, 1H), 6.20 (d, *J* = 7.95 Hz, 1H), 6.19 (d, *J* = 7.92 Hz, 1H), 4.18 (t, *J* = 6.80 Hz, 2H), 3.82 (s, 3H), 1.72−1.65 (tt, *J* = 7.16, 6.82 Hz, 2H), 1.39−1.32 (2H), 1.30−1.12 (12H), 0.80 (t, *J* = 7.18 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 Hz, $CDCl_3$): δ 163.1, 163.0, 140.8, 101.2, 100.7, 66.1, 53.4, 31.9, 29.6, 29.6, 29.5, 29.3, 29.1, 26.1, 22.7, 14.1. HRMS (FT-ICR, ESI$^+$): calcd for $C_{16}H_{27}NNaO_2$ (M + Na), 288.1940; found, 288.1931.

*2-(3-Phenylpropoxy)-6-methoxypyridine (**27b**).* By following the general procedure for ketene *N,O*-acetal synthesis via pyridine-based nucleophiles and electrophilic peroxides, as described above, 2-bromo-6-methoxypyridine (2.00 equiv, 387.7 mg, 2.00 mmol) was reacted with *n*-BuLi (2.00 equiv, 181.8 μL, 2.00 mmol, 11.0 M in hex.) and 2-((3-phenylpropyl)peroxy)tetrahydro-2*H*-pyran (**16**, 1.00 equiv, 236.3 mg, 1.00 mmol) to furnish the title molecule as a colorless oil (227.3 mg, 93%). Characterization: R_f = 0.69 (5% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39 (t, *J* = 7.88 Hz, 1H), 7.23−7.18 (m, 2H), 7.16−7.09 (m, 3H), 6.21 (t, *J* = 7.85 Hz, 2H), 4.22 (t, *J* = 6.44 Hz, 2H), 3.78 (s, 3H), 2.71 (t, *J* = 7.55 Hz, 2H), 2.06−1.98 (tt, *J* = 7.57, 6.48 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 163.1, 162.9, 141.8, 140.9, 128.5, 128.4, 125.9, 101.3, 100.9, 65.1, 53.4, 32.4, 30.8. HRMS (FT-ICR, ESI$^+$): calcd for $C_{15}H_{17}NNaO_2$ (M + Na), 266.1157; found, 266.1146.

*2-((3,7-Dimethyl-6-octenyl)oxy)-6-methoxypyridine (**27c**).* By following the general procedure for ketene *N,O*-acetal synthesis via pyridine-based nucleophiles and electrophilic peroxides, as described above, 2-bromo-6-methoxypyridine (2.00 equiv, 387.7 mg, 2.00 mmol) was reacted with *n*-BuLi (2.00 equiv, 181.8 μL, 2.00 mmol, 11.0 M in hexanes) and 2-((3,7-dimethyloct-6-en-1-yl)peroxy)-tetrahydro-2*H*-pyran (**15**, 1.00 equiv, 256.4 mg, 1.00 mmol) to furnish the title molecule as a colorless oil (240.0 mg, 91%). Characterization: R_f = 0.35 (1% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39 (t, *J* = 7.93 Hz, 1H), 6.19 (d, *J* = 7.93 Hz, 2H), 5.02 (tsept, ^3J = 7.18, ^4J = 1.49 Hz, 1H), 4.29−4.17 (m, 2H), 3.82 (s, 3H), 2.00−1.84 (m, 2H), 1.79−1.70 (m, 1H), 1.65−1.55 (m, 1H), 1.60 (d, ^4J = 1.51 Hz, 3H), 1.55−1.45 (m, 1H), 1.53 (s, 3H), 1.37−1.28 (m, 1H), 1.21−1.08 (m, 2H), 0.88 (d, *J* = 6.79 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 163.1, 163.0, 140.8, 131.2, 124.7, 101.3, 100.7, 64.4, 53.4, 37.2, 36.0, 29.6, 25.7, 25.5, 19.6, 17.7. HRMS (FT-ICR, ESI$^+$): calcd for $C_{16}H_{25}NNaO_2$ (M + Na), 286.1783; found, 286.1773.

General Procedure for Acid-Catalyzed Hydration of Indole-Based, Ketene *N,O*-Acetals (Table 8). A scintillation vial with a magnetic stir bar was charged with an aliquot of pure ketene *N,O*-acetal (**21b** or **22**, 60.0−90.0 mg) and THF (5 mL). The vial was capped with a septum, flushed with nitrogen, and allowed to stir for several minutes. To the system, water (5 mL) and 10% aq sulfuric acid (300 μL) were injected sequentially, resulting in a pronounced color change (lime green to amber brown). The reagents were left to mix for several hours at room temperature (6−10 h) before being diluted with saturated, aq potassium carbonate (3 mL), extracted with EtOAc (copious amounts used, 3×), dried with sodium sulfate, filtered, and concentrated *in vacuo* (at room temperature). The obtained dark-yellow residue was purified via flash column chromatography (15% EtOAc/Hex) to furnish 1-methylindolin-2-one (**29**), and a corresponding alcohol, in moderate yields.

*1-Methylindolin-2-one (**29**) via **21b**.* Using the general procedure for acid-catalyzed hydration of indole-based, ketene *N,O*-acetals, as described above, 2-octyloxy-1-methylindole (**21b**, 60.0 mg, 231.0 μmol) was reacted under hydrolyzing conditions (5 mL of H_2O, 300.0 μL of 10% aq H_2SO_4) for 6 h to provide 1-methylindolin-2-one (14.8 mg, 44%) and octanol (12.5 mg, 42%) as colorless oils. Characterization (of **29**): R_f = 0.19 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24−7.19 (m, 1H), 7.18−7.14 (m, 1H), 7.00−6.94 (m, 1H), 6.77−6.72 (m, 1H), 3.45 (s, 2H), 3.14 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 175.1, 145.2, 127.9, 124.5, 124.3, 122.4, 108.1, 35.8, 26.2. Spectral data matched those of a previous report.[56]

*1-Methylindolin-2-one (**29**) via **22**.* Using the general procedure for acid-catalyzed hydration of indole-based, ketene-*N,O*-acetals, as described above, 2-(octan-2-yloxy)-1-methylindole (**22**, 90.9 mg, 348.0 μmol) was reacted under hydrolyzing conditions (5 mL of H_2O, 300.0 μL of 10% aq H_2SO_4) for 10 h to provide 1-methylindolin-2-one (25.9 mg, 51%) and 2-octanol (19.6 mg, 43%) per qNMR analysis. Characterization (of **29**): see above.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02506.

^{1}H and ^{13}C spectra for substrates and novel ketene acetals (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

DCM, dichloromethane; DHP, dihydropyran; DMF, dimethylformamide; Et_2O, diethyl ether; EtOAc, ethyl acetate; Hex, hexanes; *n*-BuLi, *n*-butyllithium; NMR, nuclear magnetic resonance; qNMR, quantitative (^1H) nuclear magnetic resonance; *t*-Bu, *tert*-butyl; *t*-BuLi, *tert*-butyllithium; THF, tetrahydrofuran; THP, tetrahydropyranyl; TLC, thin-layer chromatography; TMP, 2,2,6,6-tetramethylpiperidine

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