Catalytic Aerobic Generation of Acyliminium Ions through Electron-Transfer-Mediated Carbon-Carbon Bond Activation

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Abstract: Homobenzylic amides and carbamates, upon single-electron oxidation, undergo mesolytic cleavage reactions to form acyliminium ions. Appending nucleophilic groups to these substrates results in cyclization reactions to form *N*-acylaminals. The *N*-methylquinolinium ion that serves as the photooxidant in these reactions can function as a catalyst when dioxygen is introduced into these reactions, representing a unique method for effecting catalytic, aerobic oxidations. Herein we present a full account of our studies on catalytic aerobic electron-transfer-initiated cyclization reactions of homobenzylic amides and carbamates, with particular emphasis on the roles of the amide group, the nucleophilic group, and the functionality in the tether in promoting efficient ring constructions and altering reaction mechanisms.

Keywords: C−C activation, cyclization, electron transfer, oxidation, photochemistry, radical ions

Introduction

Enhancing the electrophilicity of a functional group is most commonly achieved through coordination with an electron-deficient species (i.e., Lewis acid activation). While the utility of this approach is beyond question, functional group compatibility issues can arise when activating polyfunctional molecules that contain several acid-sensitive moieties. A complementary approach to electrophile formation proceeds through removing an electron from a functional group. Given that the propensities of functional groups to lose an electron[1] often do not correlate with their basicity, oxidative entries into electrophile formation offer unique opportunities for designing chemoselective processes[2] that are not possible through conventional acid-mediated protocols. Several oxidative methods have been developed to form electrophiles that are normally accessed through acidic processes. For example, oxocarbenium ions have been formed through the oxidation of α-stannyl ethers either electrochemically[3] or chemically with cerium(IV) reagents[4] or of α-silyl ethers under electrochemical conditions.[5] Acyliminium ions can be formed directly from tertiary amides through anodic oxidation,[6] though electrofuges such as carboxylate groups[7] or trialkylsilyl groups[8] are often employed in order to facilitate oxidation or to control the regiochemical outcome of the reaction.

Arnold's seminal studies[9] on the structural requirements for solvolytic carbon-carbon bond cleavage of photogenerated alkylarene radical cations (Figure 1) demonstrated that the proclivity for bond cleavage can be defined through Equation (1). In this relationship BDE(RC) is defined as the dissociation energy of the relevant bond in the radical cation, BDE(S) is the bond dissociation energy in the neutral substrate, $E_{pa}(S)$ is the oxidation potential of the substrate, and $E_{pa}(E)$ is the oxidation potential of the radical corresponding to the electrophilic fragment (the alkoxyalkyl radical in the illustrated reaction). Thus, the ether group at the homobenzylic position functions both to weaken the benzylic carbon-carbon bond and to stabilize the carbocationic fragment.

$$BDE(RC) = BDE(S) - E_{pa}(S) + E_{pa}(E) \qquad (1)$$

We have applied this method of carbon-carbon bond activation to the development of electron-transfer-initiated cyclization (ETIC) reactions in which a nucleophile is appended to the oxidatively generated electrophile (Figure 2). Our initial work focused on adding oxygen-based nucleophiles such as hydroxy and ether groups into oxocarbenium ions.[10] These studies showed that the cationic oxidant *N*-methylquinolinium hexafluorophosphate (NMQPF₆), when accompanied by
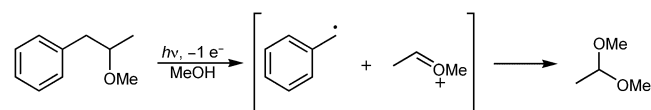
Figure 1. Benzylic carbon-carbon bond activation through single electron oxidation.
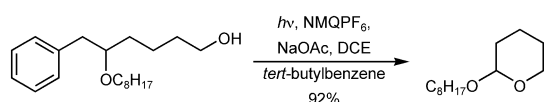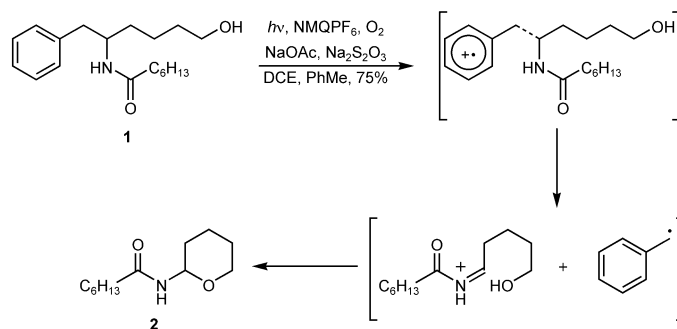
Figure 2. Prototypical ETIC reaction.
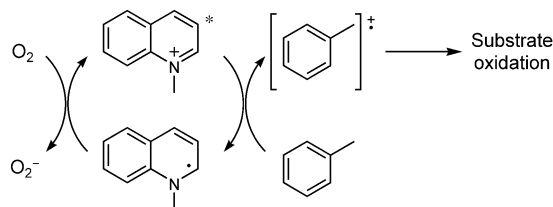
Figure 3. Aerobic single electron oxidation mediated by the *N*-methylquinolinium ion.

Figure 4. Mechanism of homobenzylic secondary amide ETIC reactions.

tert-butylbenzene as a cosensitizer, provided dramatically superior kinetics relative to the cyanoarene photooxidants used in Arnold's studies.

The need for 2 equivs. of NMQPF$_6$ to effect cyclization, however, was a drawback to our early efforts. During our search for a more efficient oxidant we became intrigued by Dinnocenzo and coworkers' spectroscopic studies[11] in which signals from the *N*-methyldihydroquinolyl radical, the one-electron reduction product of NMQ$^+$, vanished upon exposing samples to air. The authors' proposal that this result arose from the aerobic oxidation of the radical to a cation led us to speculate that NMQPF$_6$ could be used as a catalytic single-electron oxidant and that dioxygen could serve as an inexpensive and environmentally benign terminal oxidant (Figure 3). The aerobic variant of the ETIC reaction proved to be quite effective,[12] permitting us to reduce the amount of NMQPF$_6$ to 2.5 mol %, facilitating product purification, allowing us to use toluene as a cheaper and more volatile alternative to *tert*-butylbenzene as the cosensitizer, and increasing the potential scale for efficient reaction. Although the superoxide that forms in this process can cause substrate and product decomposition, its effects can be mitigated completely by including solid Na$_2$S$_2$O$_3$ in the reaction mixtures.

Our success in the early stages of this project allowed us to speculate upon methods to enhance the scope of the process. In consideration of Eq. (1) we postulated that other electron-donating groups such as amides and carbamates at the homobenzylic position should function analogously to the alkoxy group. Herein we report a full account[13] of our efforts to initiate aerobic ETIC reactions that proceed through the oxidative cleavage of homobenzylic amides and carbamates to form intermediate acyliminium ions, with an emphasis on the roles played by the amide group, the nucleophile, and the functional groups in the tether on the efficiency and mechanism of the process.

Results and Discussion

As an initial test of the ability of an amide group to promote ETIC reactions, we prepared secondary amide **1** and subjected it (Figure 4) to our standard aerobic oxidation conditions (Pyrex filter, *h*v, NMQPF$_6$, O$_2$, NaOAc, Na$_2$S$_2$O$_3$, DCE, PhMe). This reaction provided the cyclic acylaminal **2** in 75% yield, consistent with the expected sequence of arene oxidation, benzylic carbon-carbon bond cleavage to provide the corresponding acyliminium ion, and cyclization to produce the desired product.

Although the structural difference between **1** and tertiary amide **3** appears to be rather slight, the additional alkyl group lowers the oxidation potential of the amide by approximately 0.5 V[1] and alters the reaction pathway so that the amide group should be oxidized in preference to the arene. Thus we were pleased to observe the conversion of **3** to **4** in 71% yield (Figure 5). Two mechanistic pathways could account for this relatively smooth conversion. One possibility is that the amide radical cation is in equilibrium with the arene radical cation and this intermediate, although less stable, leads to rapid bond cleavage and product formation. An alternative possibility is that the amide-centered radical cation also weakens adjacent bonds and that the benzylic carbon-carbon bond cleaves in preference to the homobenzylic bond due to its lower bond dissociation energy.[14] Although these mechanisms converge in terms of their expected outcome, subsequent experiments on more highly functionalized substrates (see below) indicate that the latter explanation is more likely.

Trifluoroacetamides were shown to be ineffective at promoting ETIC reactions. This result can be explained by the reduced capacity of this group to stabilize the intermediate cationic species, translating into a large $E_{pa}(E)$, Eq. (1).

To confirm that the reaction proceeds through intermediacy of an acyliminium ion and not through a direct displacement mechanism, we prepared substrate **5**, in which a methyl group was included at the bis-homobenzylic position, as a single diastereomer. Aerobic
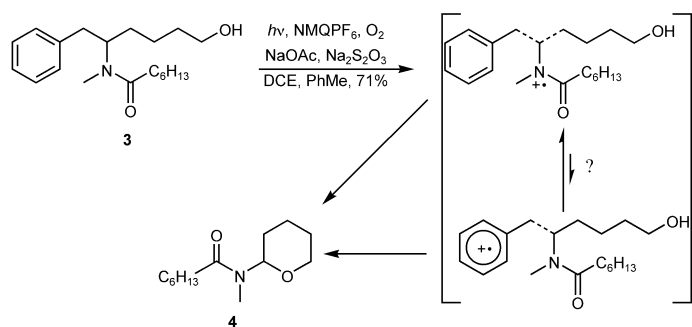
Figure 5. Mechanistic possibilities of homobenzylic tertiary amide cyclizations.
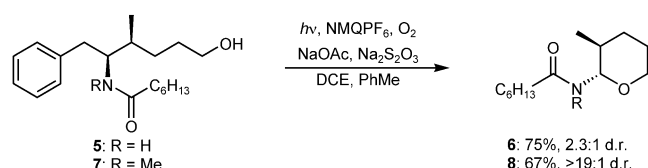

Figure 6. Diastereoselectivity in aerobic ETIC reactions.

ETIC conditions resulted in the formation of **6** in 75% yield as a 2:1 mixture of diastereomers (Figure 6) wherein the equatorial isomer, the product of stereochemical retention, was the major product. The possibility of a direct displacement followed by equilibration after cyclization was ruled out by subjecting both pure diastereomers of **6** to the reaction conditions. Although slow interconversion was observed, the rate was insufficient to account for the outcome of the cyclization. Tertiary amide **7** proved to be an extremely effective substrate with respect to stereoselectivity, producing acylaminal **8** in 67% yield as a single isomer. We believe that this outcome arises from the enhanced steric demands of tertiary amides relative to secondary amides, strongly disfavoring an axial orientation in the transition state.

Previous work in our group[10] showed that acetals are effective nucleophiles in these reactions, with the THP ether functioning as a surrogate for a hydroxy group. Using acetals as hydroxyl-group equivalents facilitates the handling of polar amide-containing substrates, and creates interesting opportunities for utilizing nucleophiles that would not be stable in an unprotected state. In conjunction with our synthetic efforts toward mycalamide B[15] (Figure 7), we needed to design a functional equivalent of a formaldehyde acetal to add into an acyliminium ion. We reasoned that this could be accomplished by employing a mixed acetal of formaldehyde in which the distal alkyl group could readily be lost as a cation. Thus SEM-ether **9** was prepared and subjected to aerobic ETIC conditions. Instead of yielding the desired cyclization product, this reaction provided the surprisingly stable *N*-acyl hemiaminal **10** in 69% yield. Since this reaction proceeded to completion within 4 h and our initial work demonstrated that bimolecular reactions with water in the absence of a competent intramolecular nucleophile occur very slowly, we postulated that the initial cyclization proceeded as expected. However, given that the resulting localized oxonium ion intermediate can revert to a delocalized acyliminium ion, we concluded that trimethylsilylethyl group departure is slow and the addition of adventitious water to the acyliminium is rapid, leading to the observed product. Thus, increasing the rate of cation loss was expected to favor the formation of the desired product. We prepared tetrahydrofuranoxymethyl ether **11**, in which the oxonium ion intermediate can decompose through the loss of the stabilized 2-tetrahydrofuryl cation, and subjected it to aerobic ETIC conditions. In accord with our analysis we isolated acylaminal **12** in 79% yield, demonstrating that the fate of the oxonium ion intermediate can be controlled in a rational manner through tuning carbocation stability. Carbamate groups were also shown to react in an identical manner to amides in this series.
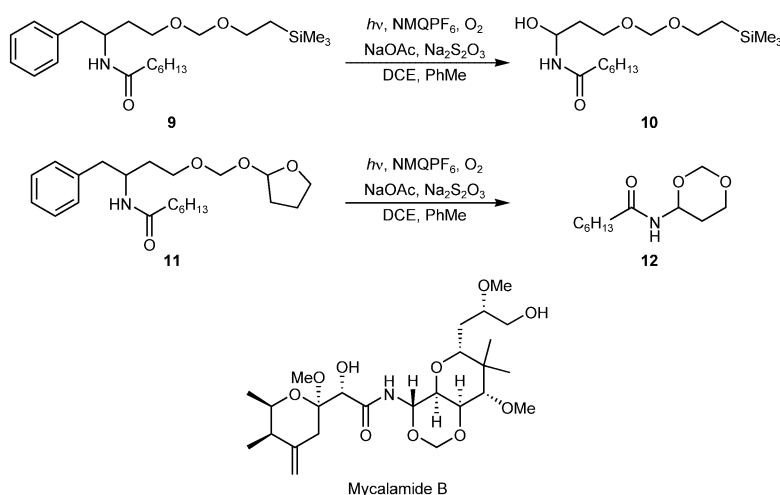

Figure 7. Development of a formaldehyde hemiacetal surrogate.
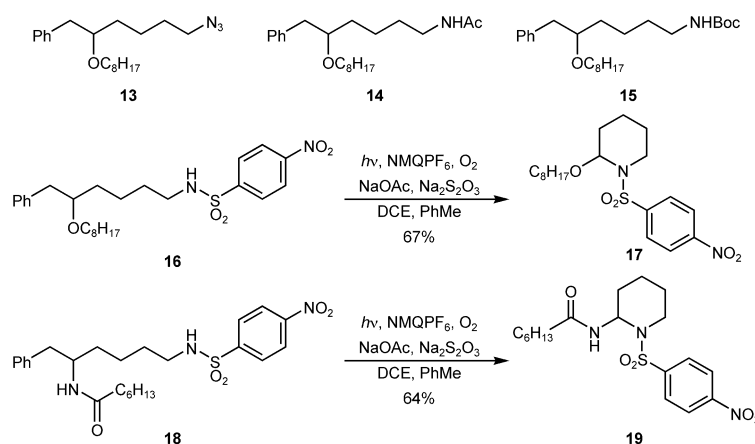
Figure 8. Nitrogen-based nucleophiles in ETIC reactions.

Toward the objective of preparing cyclic *N,N*-acylaminals of the type that are present in several glycosidase inhibitors,[16] we needed to identify a nitrogen-based nucleophile that reacts efficiently under ETIC conditions. In order to avoid the difficulties associated with handling polar amides, we screened nucleophiles using homobenzylic ethers. Alkyl azides have been shown to add to oxocarbenium ions under Lewis acidic conditions,[17] albeit rather slowly. Under aerobic ETIC conditions, however, we observed no reaction of azide **13** (Figure 8), suggesting that the alkyl azides are not sufficiently nucleophilic to react with the transiently generated oxocarbenium ion. Amide **14** and carbamate **15** decomposed upon radical-cation formation. Nitrobenzenesulfonamide **16**, though, cyclized to provide *N,O*-aminal **17** in a respectable 67% yield. Moreover, amide **18** produced *N,N*-acylaminal **19** in 64% yield. The kinetic superiority of sulfonamide groups relative to amide and carbamate nucleophiles is consistent with the absence of a rehybridization process occurring in the cyclization transition state. Since nitrobenzenesulfonamides are easy to handle and deprotect,[18] the products of these transformations could prove to be quite useful.

In consideration of future synthetic objectives, we studied the effects of introducing oxygen groups at the bis-homobenzylic position of our substrates. This structural alteration is expected to destabilize the intermediate acyliminium ion, potentially slowing or completely stopping the reactions through the inductive effect. Therefore, we were pleased to observe the formation of acylaminal **21** in 63% yield (Figure 9) as a 2:1 mixture of diastereomers from the aerobic ETIC reaction of secondary carbamate **20**, again consistent with the intermediacy of an acyliminium ion. Tertiary carbamate **22**, however, decomposed upon oxidation. We postulated that tethering the acyliminium ion to the homobenzylic oxygen would improve the stereoselectivity of the process by forcing the reaction to proceed through a bicyclic transition state. Thus, oxazolidine **23** was
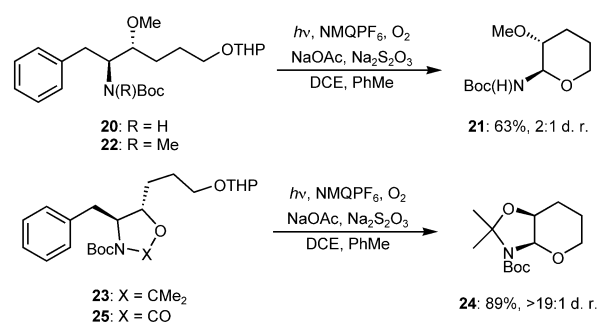

Figure 9. Incorporation of oxygen at the bis-homobenzylic position.

exposed to oxidation conditions, providing bicycle **24** as a single diastereomer in 89% yield. In contrast, oxazolidinone **25** was inert toward oxidation, presumably as a result of the enhanced inductive deactivation conferred by the ester-like bis-homobenzylic substituent relative to an ether-like substituent.

The contrasting behavior of **22** and **23** illustrates an interesting and important stereoelectronic effect in radical cleavage reactions.[19] Although both substrates can formally be considered to be tertiary carbamates with an adjacent ether substituent, the oxazolidine reacts smoothly whereas the acyclic analogue decomposes. We postulate that this result arises from preferential oxidation of the tertiary carbamate over the arene, as expected on the basis of an analysis of the relative oxidation potentials of these groups. In contrast to previous cyclizations of tertiary carbamates, the homobenzylic carbon-carbon bond of **22** is considerably activated toward fragmentation by virtue of the bond-weakening effects of the donation of the lone pairs of the oxygen of the bis-homobenzylic methoxy group into the σ*-orbital of the labile bond (Figure 10). Thus, the reaction proceeds through cleavage of the undesired carbon-carbon bond. In confirmation of this hypothesis,

we isolated in low yield the THP ether of methyl 4-hydroxybutyrate from the oxidation of **22**. The structural constraints of the oxazolidine, however, do not allow significant overlap between the oxygen lone pairs and the σ*-orbital of the homobenzylic carbon-carbon bond. The SOMO of the carbamate group also lacks overlap with this bond, preventing a low energy pathway to form the acyliminium ion directly. The benzylic carbon-carbon bond, however, can align with the carbamate SOMO for facile cleavage. The successful cyclization of **23** also implies that no particular importance can be assigned to the oxidation of the arene and that Eq. (1) applies regardless of the electrophore of the molecule. This finding should prove to be quite useful in the design of new modes of radical ion cleavage.

The ability to effect cyclizations into α-alkoxyacyliminium ions provided us with sufficient precedent to investigate an oxidative approach to the amidotrioxadecalin ring system, an integral structural feature in mycalamide B. Our initial approach (Figure 11) to this system used the trimethyl ether of glucal (**26**) as the core for the tetrahydropyran ring of the trioxadecalin system. Conversion of **26** to cyclization substrate **27** was accomplished through a six-step sequence. Application of our aerobic ETIC conditions to **27** resulted in a remarkably efficient 94% yield of **28** as a 10:1 mixture of diastereomers at the acylaminal center. Interestingly, the conformation of the major product places the carbamate in an equatorial orientation and most of the substituents on the tetrahydropyran ring in axial orientations.
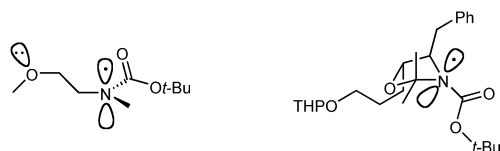
Figure 10. Optimal geometrical orientations for homobenzylic bond cleavage in acyclic systems and for benzylic bond cleavage in cyclic systems.
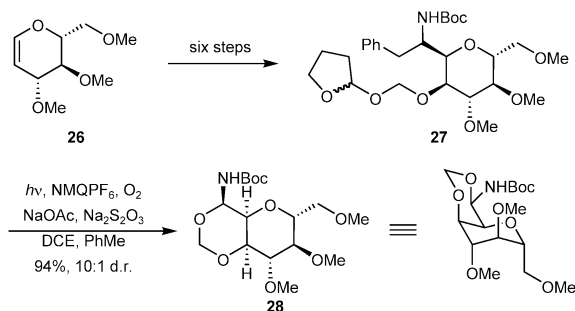
Figure 11. Aerobic formation of the amidotrioxadecalin ring system.

Summary and Conclusions

We have demonstrated that aerobic single-electron oxidation conditions can be applied to the formation of acyliminium ions from homobenzylic amides and carbamates. These studies highlight several important aspects of ETIC chemistry that are useful in considering the viability of a particular reaction. The role of the homobenzylic substituent is to weaken the benzylic carbon-carbon bond and to stabilize the carbocation that forms upon fragmentation. Both secondary and tertiary amides are effective substituents, although reactions of tertiary amides appear to proceed through amide oxidation rather than arene oxidation. This indicates that the site of oxidation is inconsequential. Trifluoroacetamides are ineffective at promoting these reactions as a consequence of their limited capacity to stabilize the carbocationic intermediate. This lack of reactivity could, in principle, be overcome if the benzylic carbon-carbon bond dissociation energy is lowered through benzylic substitution, as we have reported recently[20] for related systems. With respect to the nucleophilic component, acetals can be used as functional surrogates for a hydroxy group to facilitate starting material handling and to design unique transformations, such as nucleophilic attack by a formal equivalent of a formaldehyde hemiacetal. The intermediate oxonium ions in these cyclizations, however, are unstable with respect to delocalized acyliminium ion, mandating that the electrofugal group of the acetal be sufficiently stable to depart rapidly. Tetrahydrofuranyl and tetrahydropyranyl ethers are particularly well suited for this role. Nitrogen-based nucleophiles must be sufficiently reactive to combine with a transiently formed electrophile while being inert toward single-electron oxidation. Due to their high oxidation potentials and sp^3-hybridized nitrogen atoms, sulfonamides are effective nitrogen-based nucleophiles and have been used in the synthesis of *N,N*-acylaminals. Although the presence of a bis-homobenzylic ether group leads to decomposition of tertiary amide substrates because of competitive homobenzylic bond cleavage, oxazolidines undergo very efficient cyclization reactions. A stereoelectronic effect has been proposed to account for this outcome. These studies have shown that our aerobic generation of acyliminium ions are quite versatile and tolerant to the presence of other functional groups in cyclization substrates. The culmination of this work can be seen in its application to the synthesis of the highly oxygenated, acid-sensitive amidotrioxadecalin ring system. We are currently exploiting the unique features of these aerobic reactions for the synthesis of natural products and other biologically active compounds.

Experimental Section

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300

spectrometers at 300 MHz and 75 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak or the internal standard tetramethylsilane were used as reference values. For ^{1}H NMR: $CDCl_3 = 7.27$ ppm, $TMS = 0.00$. For ^{13}C NMR: $CDCl_3 = 77.23$, $TMS = 0.00$. For proton data: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets, dt = doublet of triplets, ddt = doublet of doublets of triplets; br = broad; m = multiplet; app t = apparent triplet; app q = apparent quartet; app p = apparent pentet.

High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Gygnus 100 spectrometer. Analytical thin layer chromatography (TLC) was performed on E. Merck pre-coated (25 nm) silica gel 60F-254 plates. Visualization was done under UV (245 nm). Flash column chromatography was preformed using ICN SiliTech 32 – 63 60µ silica gel. Reagent grade ethyl acetate and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. Reagent grade methylene chloride (CH_2Cl_2), dichloroethane ($C_2H_4Cl_2$), acetonitrile (CH_3CN), benzene and toluene were distilled from CaH_2. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketal prior to use. Anhydrous N,N-dimethylformamide (DMF), methanol (MeOH), and dimethyl sulfoxide (DMSO) were purchased from Aldrich and used as is. All reactions were conducted under anitrogen atmosphere, unless otherwise specified.

Representative Catalytic Aerobic Cyclization Protocol; Acylaminal 2

To **1** (89 mg, 0.306 mmol) in dichloroethane (10 mL) and toluene (2 mL) in a borosilicate flask at 20 ^{0}C were added N-methylquinolinium hexafluorophosphate (2 mg, 7 µmol), sodium acetate (178 mg, 2.17 mmol), and sodium thiosulfate (178 mg, 1.13 mmol). The mixture was stirred and irradiated at a distance of 4 cm for 3 h at room temperature while bubbling air gently. The reaction mixture was filtered, concentrated, and purified by flash chromatography (50% EtOAc in hexanes) to provide **2**; yield: 45 mg (75%); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 6.05$ (d, $J = 7.9$ Hz, 1H), 5.09 (dt, $J = 8.3$, 2.3 Hz, 1H), 3.96 (m, 1H), 3.58 (m, 1H), 2.16 (m, 1H) 1.64 – 1.26 (m, 10H), 0.87 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 172.9$, 77.8, 36.9, 31.7, 31.5, 25.3, 25.2, 23.0, 22.5, 22.3, 14.0; IR (neat): $\nu = 3286$, 2950, 2855, 1660, 1544, 1453, 1208, 1083, 1032, 903 cm^{-1}; HRMS (EI): calcd. for $C_{11}H_{21}NO_2$: 199.1572; found: 199.1588.

Acylaminal 4

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **3** (55 mg, 0.178 mmol), dichloroethane (5 mL), toluene (1 mL), N-methylquinolinium hexafluorophosphate (1 mg, 2 µmol), sodium acetate (100 mg, 1.2 mmol), and sodium thiosulfate (100 mg, 0.63 mmol). The mixture was irradiated for 4 h. Chromatographic purification (50% EtOAc in hexanes) provided **4** which was analyzed as a 1:1 mixture of amide rotamers; yield 27 mg (71%); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 5.64$ (dd, $J = 5.6$, 3.3 Hz, 1H), 4.82 (dd, $J = 8.5$, 1.8 Hz, 1H), 4.02

(bt, $J = 12.9$ Hz, 2H) 3.58 (m, 1H), 2.91 (s, 3H), 2.88 (s, 3H), 2.41 – 2.25 (m, 4H), 1.99 – 1.24 (m, 12H), 0.88 (t, $J = 5.5$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 173.3$, 85.4, 81.2, 68.4, 34.1, 33.5, 31.7, 29.7, 29.2, 28.6, 27.3, 25.3, 25.2, 25.1, 24.5, 23.5, 23.4, 23.1, 22.6, 14.0; IR (neat): $\nu = 2933$, 2855, 1660, 1462, 1410, 1372, 1316, 1079, 1036, 911 cm^{-1}; HRMS (EI): calcd. for $C_{12}H_{23}NO_2$: 213.1728; found: 213.1732.

Acylaminal 6

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **5** (64 mg, 0.21 mmol), dichloroethane (5 mL), toluene (1 mL), N-methylquinolinium hexafluorophosphate (2 mg, 7 µmol), sodium acetate (120 mg, 1.5 mmol), and sodium thiosulfate (120 mg, 0.76 mmol). The mixture was irradiated for 2.5 h. Chromatographic purification (30% hexanes in EtOAc) provided **6** as a partially separable 2.3:1 mixture of *anti-* and *syn*-diastereomers; yield: 32 mg (72%). *Syn*-diastereomers, faster eluting: ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 5.96$ (bd, $J = 7.65$, 1H), 5.31 (dd, $J = 3.1$, 6.0 Hz, 1H), 3.85 (m, 1H), 3.67 (m, 1H), 2.21 (t, $J = 7.4$ Hz, 2H), 1.98 – 1.31 (m, 13H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.90 (t, $J = 1.7$ Hz, 3H); ^{1}H NMR (300 MHz, CDCl$_3$/D$_2$O): $\delta = 5.31$ (d, $J = 2.4$ Hz, 1H), 3.85 (m, 1H), 3.67 (m, 1H), 2.21 (t, $J = 7.4$ Hz, 2H), 1.98 – 1.31 (m, 13H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.90 (t, $J = 1.7$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 173.0$, 79.1, 65.7, 37.1, 36.39, 31.92, 31.61, 29.0, 25.4, 22.5, 21.8, 14.1, 13.1; IR (neat): $\nu = 3440$, 2954, 2851, 1655, 1466, 1075, 997, 731 cm^{-1}; HRMS (EI): calcd. for $C_{12}H_{23}NO_2$: 213.1728; found: 213.1731. *Anti*-diastereomer, slower eluting: ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 5.75$ (bs, 1H), 4.79 (t, $J = 9.5$ Hz, 1H), 3.57 (m, 1H), 3.00 (m, 1H), 2.20 (t, $J = 7.15$ Hz, 2H), 1.90 (m, 1H), 1.63 – 1.26 (m, 12H), 0.89 (m, 6H); ^{1}H NMR (300 MHz, CDCl$_3$/D$_2$O): $\delta = 4.79$ (d, $J = 9.3$ Hz, 1H), 3.57 (m, 1H), 3.00 (m, 1H), 2.20 (t, $J = 7.2$ Hz, 2H), 1.90 (m, 1H), 1.63 – 1.26 (m, 12H), 0.89 (m, 6H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 173.3$, 82.9, 67.8, 37.1, 36.4, 32.1, 31.6, 26.0, 25.4, 22.5, 17.4, 14.1; IR (neat): $\nu = 3441$, 2955, 2852, 1656, 1466, 1075 cm^{-1}; HRMS (EI): calcd. for $C_{12}H_{23}NO_2$: 213.1728; found: 213.1731.

Acylaminal 8

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **7** (98 mg, 0.31 mmol), dichloroethane (10 mL), toluene (2 mL), N-methylquinolinium hexafluorophosphate (2 mg, 7 µmol), sodium acetate (178 mg, 2.2 mmol), and sodium thiosulfate (178 mg, 1.1 mmol). The mixture was irradiated for 3 h. Purification by flash chromatography (50% EtOAc in hexanes) provided **8** which was analyzed as a 1:1 mixture of amide rotamers; yield: 47 mg (67%); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 5.36$ (d, $J = 9.8$ Hz, 1H), 4.45 (d, $J = 9.4$ Hz, 1H), 4.02 (m, 2H), 3.54 (m, 2H), 2.91 (d, $J = 11.8$ Hz, 3H), 2.31 (m, 3H), 1.99 – 1.25 (m, 6H), 0.90 (m, 3H), 0.80 (m, 3H); ^{1}H NMR (300 MHz, DMSO, 378 K): $\delta = 4.85$ (bs, 1H), 4.02 (m, 2H), 3.54 (m, 2H), 2.91 (d, $J = 11.8$ Hz, 3H), 2.31 (m, 3H), 1.99 – 1.25 (m, 6H), 0.90 (m, 3H), 0.80 (m, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 174.3$, 90.9, 86.0, 68.5, 34.3, 33.7, 33.3, 32.5, 32.2, 31.9, 26.4, 26.1, 25.4, 22.7, 17.0, 16.7, 14.1; IR (neat): $\nu = 2952$, 2853, 1654,

1456, 1073, 1005 cm^{-1}; HRMS (EI): calcd. for C$_{13}$H$_{25}$NO$_2$: 227.1885; found: 227.1891.

N-Acylhemiaminal 10

This reaction was run according to the representative catalytic protocol with the following quantities of reagents: **9** (0.11 g, 0.28 mmol), dichloroethane (6 mL), *N*-methylquinolinium hexafluorophosphate (4.0 mg, 0.01 mmol), NaOAc (0.22 g, 200 wt %), Na$_2$S$_2$O$_3$ (0.22 g, 200 wt %), and toluene (1 mL). The mixture was irradiated for 4 h. The reaction mixture was filtered through a small plug of silica, and concentrated under reduced pressure. Purification by column flash chromatography (80% EtOAc in hexanes) provided **10**; yield: 60 mg (67%); ^{1}H NMR (300 MHz, CD$_2$Cl$_2$): δ = 6.85 (br, 1H), 5.44 – 5.38 (m, 1H), 4.65 (s, 2H), 3.94 (d, *J* = 3.2 Hz, 1H), 3.82 – 3.75 (m, 1H), 3.67 – 3.54 (m, 3H), 2.14 (t, *J* = 7.3 Hz, 2H), 1.92 – 1.84 (m, 2H), 1.63 – 1.53 (m, 2H), 1.36 – 1.24 (m, 4H), 0.96 – 0.87 (m, 5H), 0.02 (s, 9H); ^{13}C NMR (75 MHz, CD$_2$Cl$_2$): δ = 175.1, 95.3, 73.8, 65.6, 63.9, 37.1, 34.7, 31.7, 25.4, 22.7, 18.4, 14.0, − 1.4; IR (neat): ν = 3299, 2955, 1654, 1538, 1249, 1060 cm^{-1}; LRMS (EI): *m/z* = 320, 302, 262, 246, 232, 202, 188, 172.

Acylaminal 12

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **8** (90 mg, 0.25 mmol), dichloroethane (6 mL), NMQPF$_6$ (3.5 mg, 0.01 mmol), NaOAc (0.18 g, 200 wt %), Na$_2$S$_2$O$_3$ (0.18 g, 200 wt %), 4 Å molecular sieves (0.18 g, 200 wt %) and toluene (1 mL). Air was gently irradiated for 4 h. Purification by column flash chromatography (50% EtOAc in hexanes) provided **12**; yield: 39 mg (79%)M; ^{1}H NMR (300 MHz, CD$_2$Cl$_2$): δ = 5.92 (br, 1H), 5.43 (td, *J* = 10.0, 2.8 Hz, 1H), 5.05 (d, *J* = 6.5 Hz, 1H), 4.83 (d, *J* = 6.5 Hz, 1H), 4.15 (app dd, *J* = 11.6, 4.9 Hz, 1H), 3.79 (td, *J* = 11.7, 2.8 Hz, 1H), 2.22 (t, *J* = 7.3 Hz, 2H), 1.91 – 1.78 (m, 1H), 1.75 – 1.60 (m, 3H), 1.35 – 1.26 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 172.7, 92.8, 77.2, 65.9, 36.7, 32.1, 31.3, 25.0, 22.4, 13.9; IR (neat): ν = 3325, 2927, 1661, 1540, 1015 cm^{-1}; HRMS (EI): calcd. for C$_{10}$H$_{19}$NO$_3$ (M$^+$): 201.1365; found: 201.1361.

Acylaminal 17

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **16** (55 mg, 0.11 mmol), dichloroethane (5 mL), toluene (1 mL), *N*-methylquinolinium hexafluorophosphate (2 mg, 7 μmol), sodium acetate (100 mg, 1.2 mmol), and sodium thiosulfate (100 mg, 0.63 mmol). The mixture was irradiated for 5 h. Purification by flash chromatography (10% EtOAc in hexanes) provided **17**; yield: 31 mg (68%); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.35 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 8.9 Hz, 2H), 5.22 (m, 1H), 3.61 (dd, *J* = 2.9, 10.0 Hz, 1H), 3.36 (m, 2H), 3.07 (t, *J* = 2.7, 10.1 Hz, 1H), 1.89 (m, 1H), 1.62 – 1.23 (m, 18H), 0.88, (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 130.1, 124.2, 84.6, 67.9, 63.2, 41.5, 33.1, 29.9, 29.6, 29.5, 26.4, 24.8, 22.7, 21.2, 18.1, 14.3, 14.1; IR (neat): ν = 3561, 3101, 2924, 2855, 1604, 1535, 1466, 1350, 1165, 1105, 937, 847, 744 cm^{-1}; HRMS (EI): calcd. for C$_{19}$H$_{30}$N$_2$O$_5$S: 398.1875; found: 398.1868.

N,N-Aminal 19

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **18** (40 mg, 0.084 mmol), dichloroethane (5 mL), toluene (1 mL), *N*-methylquinolinium hexafluorophosphate (2 mg, 7 μmol), sodium acetate (100 mg, 1.2 mmol), and sodium thiosulfate (100 mg, 0.63 mmol). The mixture was irradiated for 5 h. Purification by flash chromatography (10% EtOAc in hexanes) provided **19**; yield: 21 mg (64%); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.30 (d, *J* = 8.9 Hz, 2H), 8.04 (d, *J* = 8.9 Hz, 2H), 6.10 (m, 1H), 5.90 (m, 1H), 3.80 (m, 1H), 2.91 (dt, *J* = 8.3, 3.2 Hz, 1H), 1.79 (m, 4H), 1.22 (m, 10H), 0.84 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 172.0, 150.0, 146.0, 128.8, 124.5, 58.4, 42.0, 36.6, 31.4, 31.1, 25.2, 22.4, 18.8, 14.0; IR (neat): ν = 3313, 2939, 2861, 1650, 1527, 1354, 1147, 1097, 924, 740 cm^{-1}; HRMS (EI): calcd. for C$_{17}$H$_{26}$N$_3$O$_5$S: 384.1593; found: 384.1583.

Acylaminal 21

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **20** (55 mg, 0.13 mmol), dichloroethane (5 mL), toluene (1 mL), *N*-methylquinolinium hexafluorophosphate (2 mg, 7 μmol), sodium acetate (100 mg, 1.2 mmol), and sodium thiosulfate (100 mg, 0.63 mmol). The mixture was irradiated for 5 h. Chromatographic purification (30% acetone in hexanes) provided **21** as a separable 2:1 mixture of *anti-* and *syn-*diastereomers; yield: 19 mg (63%). *Anti*-diastereomer, faster eluting: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.70 (bs, 1H), 4.90 (bd, *J* = 9.4 Hz, 1H), 3.93 (m, 1H), 3.53 (dt, *J* = 2.3, 9.5 Hz, 1H), 3.38 (s, 3H), 3.31 (m, 1H), 2.11 (m, 1H), 1.80 – 1.25 (m, 12H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 155.3, 79.8, 75.5, 66.2, 56.7, 28.4, 25.5, 20.3; IR (neat): ν = 3443, 3338, 2930, 1719, 1490, 1367, 1163, 1064, 984, 878 cm^{-1}; HRMS (EI): calcd. for C$_{11}$H$_{21}$NO$_4$: 231.1471; found: 231.1471. *Syn*-diastereomer, slower eluting: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.11 (bs, 1H), 4.66 (t, *J* = 8.4 Hz, 1H), 3.88 (m, 1H), 3.50 (dt, *J* = 2.2, 9.2 Hz, 1H), 3.38 (s, 3H), 2.98 (m, 1H), 2.22 (m, 1H), 1.68 – 1.44 (m, 12H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 155.3, 83.0, 80.4, 66.5, 56.7, 29.9, 28.5, 24.8; IR (neat): ν = 3444, 3339, 2931, 1719, 1491, 1367, 1163, 1064, 984, 878 cm^{-1}; HRMS (EI): calcd. for C$_{11}$H$_{21}$NO$_4$: 231.1471; found: 231.1484.

Acylaminal 25

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **24** (100 mg, 0.23 mmol), dichloroethane (10 mL), toluene (1 mL), *N*-methylquinolinium hexafluorophosphate (2 mg, 7 μmol), sodium acetate (200 mg, 2.4 mmol), and sodium thiosulfate (200 mg, 1.3 mmol). The mixture was irradiated for 2 h. Chromatographic purification (45% EtOAc in hexanes) provided **25** as a single diastereomer; yield: 53 mg (85%); ^{1}H NMR (300 MHz, CDCl$_3$, 323 K): δ = 5.15 (bs, 1H), 3.97 (m, 1H), 3.88 (m, 2H), 3.43 (dt, *J* = 2.8, 8.5 Hz, 2H), 2.13 – 2.08 (m, 2H), 1.95 – 1.38 (m, 17H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 151.9, 128.4, 100.2, 93.9, 83.2, 71.2, 63.7, 31.5, 28.4, 24.8, 22.5, 19.7; IR (neat): ν = 2974, 2934, 2871, 1706, 1457, 1394, 1263,

1180, 1081, 1017 cm^{-1}; HRMS (EI): calcd. for $C_{12}H_{20}NO_4$: 242.1392; found: 242.1402.

Amidotrioxadecalin 28

This reaction was run according to the representative catalytic aerobic protocol with the following quantities of reagents: **27** (29 mg, 0.05 mmol), DCE (6 mL), NMQPF$_6$ (0.8 mg, 0.003 mmol), NaOAc (58 mg, 200 wt %), Na$_2$S$_2$O$_3$ (58 mg, 200 wt %), molecular sieves (58 mg, 200 wt %) and toluene (1 mL). The suspension was stirred at room temperature for 30 min, then irradiated for 2 h. Purification by flash chromatography (50% EtOAc in hexanes) provided **28** as a 10:1 mixture of diastereomers; yield: 18 mg (94%). *Major diastereomer:* ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 5.97$ (d, $J = 9.7$ Hz, 1H), 5.12 (d, $J = 6.7$ Hz, 1H), 5.08 (dd, $J = 9.7, 1.4$ Hz, 1H), 4.84 (d, $J = 6.7$ Hz, 1H), 4.17 (dt, $J = 7.8, 4.0$ Hz, 1H), 3.92 (dd, $J = 1.8, 1.8$, 1H), 3.72 (dd, $J = 1.8, 1.8$ Hz, 1H), 3.62 – 3.60 (m, 2H), 3.50 (dd, $J = 3.8, 2.5$ Hz, 1H), 3.47 (s, 3H), 3.47 (s, 3H), 3.42 (s, 3H), 3.31 – 3.29 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, CDCl$_3$): $\delta = 154.9, 91.6, 80.7, 80.5, 79.6, 76.8, 74.5, 73.5, 71.5, 65.5, 59.3, 58.4, 57.7, 28.3$; IR (neat): $\nu = 2922, 1724, 1500$ cm^{-1}; $[\alpha]^{25}_D$: $+17.87$ (c 0.62 CHCl$_3$); HRMS (ES): calcd. for $C_{16}H_{29}NO_8Na$ (M + Na): 386.1791; found: 386.1828. *Minor diastereomer:* ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 5.44$ (dd, $J = 9.3, 8.6$ Hz, 1H), 5.17 (d, $J = 9.3$ Hz, 1H), 5.10 (d, $J = 7.0$ Hz, 1H), 4.88 (d, $J = 7.0$ Hz, 1H), 4.14 (dd, $J = 9.6, 6.3$ Hz, 1H), 3.87 (app t, $J = 9.0$ Hz, 1H), 3.76 (dd, $J = 9.6, 6.3$ Hz, 1H), 3.70 – 3.64 (m, 1H), 3.64 (s, 3 H), 3.75 – 3.50 (m, 2H), 3.54 (s, 3H), 3.38 (s, 3H), 3.27 – 3.20 (m, 1 H), 1.47 (s, 9 H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 155. 86.9, 81.1, 79.8, 79.0, 78.7, 77.9, 73.5, 71.2, 70.9, 60.8, 60.7, 59.3, 30.0, 28.5$; $[\alpha]^{25}_D$: $+47.53$ (c 0.65 CHCl$_3$).

Acknowledgements

References and Notes

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