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Reaction Discovery Using Microfluidic-Based Multidimensional Screening of Polycyclic Iminium Ethers

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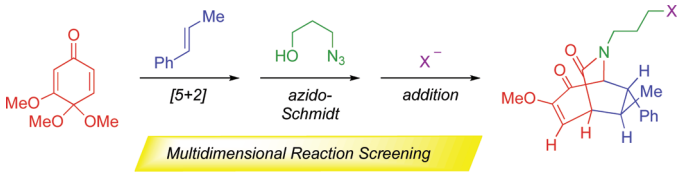

Polycyclic iminium ethers are ambident electrophilic intermediates that react with a range of nucleophiles in a highly condition-dependent manner to afford densely functionalized lactams. In an effort to expand the scope of reactivity and assist in the generation of new chemotypes from these intermediates, several iminium ethers were subjected to reaction screening using an automated microfluidics reaction platform. Application of this approach led to the discovery of several interesting reaction pathways involving the iminium ether intermediates that will be described.

Introduction

Iminium ethers have shown great utility in the synthesis of functionalized heterocycles.[1] Acyclic iminium ethers are typically formed through *O*-alkylation of amides, while cyclic and polycyclic versions can be formed through the direct *N*-alkylation of oxazolines and dihydrooxazines[2] or by reaction of ketones with hydroxyalkyl azides (Figure 1).[3] The ambident electrophilic nature of these species gives access to different reaction pathways within a single substrate.[1,4] This feature makes iminium ethers particularly attractive substrates for reaction screening, as there is a possibility for multiple chemotypes to arise from a single substrate. In addition, the availability of a wide range of structurally diverse iminium ethers and their ability to react with a wide selection of nucleophiles further increases the potential to generate unique sets of highly functionalized products.

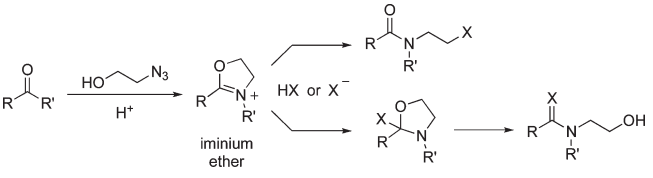

FIGURE 1. Synthesis and reactivity of cyclic iminium ethers.

An ongoing goal of the Kansas laboratory is to increase the variety of chemotypes that can be accessed from iminium ethers. As transformations of iminium ethers have been shown to be highly condition-dependent, we considered that multidimensional reaction screening[5] developed by the BU

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laboratory would provide an attractive strategy to address this need. Nucleophile selection, iminium ether stability, reaction solvent, time, and temperature, among other factors, have been shown to influence the outcome of reactions of iminium ethers.[4a,6] Accordingly, a systematic screening of iminium ether substrates, reaction partners, additives, and reaction conditions in an array format would facilitate access to the greatest breadth of substrate reactivity. Moreover, use of an automated microfluidic reaction screening platform allows for the reactions to be completed on an analytical scale in continuous succession, resulting in considerable savings of both time and material. Herein, we report a series of multidimensional reaction screens completed utilizing both a relatively simple bicyclic iminium ether and a densely functionalized bicyclo[3.2.2] scaffold.[7]

Results and Discussion

Selection and Synthesis of Iminium Ethers. We initially sought to identify a complex scaffold upon which to examine iminium ether reactivity. To this end, a set of five multifunctional ketones **1**−**5**[7−11] were reacted with 3-azido-1-propanol under acidic conditions, followed by hydrolysis and spectroscopic analysis (Figure 2).[3c] Of these, only bicyclo[3.2.1]octanoid **5** led to an appreciable quantity of the desired lactam product. Characterization of the resulting lactams revealed formation of a mixture of regioisomers arising from differential migration of the carbon centers adjacent to the bridgehead ketone. Modification of the workup allowed for isolation of the iminium ether intermediates as a mixture of regioisomers. Thus, the iminium ethers derived from **5** were deemed suitable complex substrates for the present study.

As previously reported, bicyclo[3.2.1]octanoid **5** was derived from a [5 + 2] cycloaddition between a quinone monoketal and a styrene component.[7,12] Use of this methodology allowed for the synthesis of four additional bicyclo[3.2.1]octanoid scaffolds, which were also evaluated for their performance in the azido-Schmidt reaction with 3-azido-1-propanol (Table 1). Bicyclo[3.2.1]octanoid scaffolds bearing an allyl group in the R_1 position failed to react, but when R_1 was a hydrogen atom, a mixture of regioisomers could be isolated.[13] Substrate **5**, synthesized from *trans*-β-methylstyrene, gave both the greatest overall yield (88%) and the best regioselectivity (3:1) in this reaction.

The reaction of **5** was further investigated to determine the effect of the hydroxyalkyl azide, solvent, and temperature on regioselectivity of the reaction (Table 2). Preliminary acid promoter screening revealed that significant conversion to

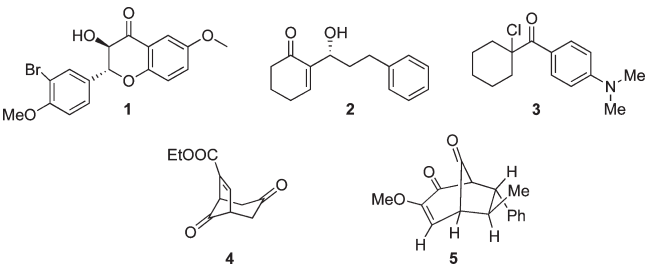

FIGURE 2. Substrates surveyed in the azido-Schmidt reaction.

product was only observed with promoters in which triflic acid was released; triflic acid itself afforded full conversion.[14] A marked increase in the regioselectivity was observed when 2-azido-1-ethanol was substituted for 3-azido-1-propanol. Further, the regioselectivity also showed notable temperature dependence when 2-azido-1-ethanol was employed. Conversely, this effect was not observed in reactions using 3-azido-1-propanol. Changes in solvent appeared to have little, if any, effect on the regioselectivity.

Unfortunately, iminium ethers arising from reaction of **5** and **10** (Table 2, entry 1−6) proved to be unstable even as a mixture of regioisomers and were not used further in this study. Iminium ethers **14a** and **14b** were obtained as a 3:1 mixture of regioisomers by carrying out the hydroxyalkyl azide addition step according to the conditions noted in entry 12 of Table 2 followed by a water wash. It has been previously shown that iminium ethers can be purified by column chromatography, but the compounds under investigation proved unstable to silica gel chromatography. Thus, the regioisomeric mixture of **14a/14b** was used without further purification in multidimensional screening experiments (Scheme 1). The regioisomeric ratio was determined by spectroscopic analysis and by conversion to **13a/13b** upon treatment with mild aqueous base. In all but a few cases, the products derived from the **14a/14b** mixture were separable by silica gel chromatography.

Previous work has shown that the regiochemical outcome of ring expansion reactions of hydroxyalkyl azides and α-substituted cyclic ketones is dependent on both the influence of the steric environment and the electronic nature of the migrating centers.[13] Thus, although reactions of methyl and ethyl α-substituted ketones were generally nonselective, migration of the more highly substituted carbon was favored when bulkier substituents were used. In contrast, when inductively electron-withdrawing substituents were placed α to the ketone, selective (up to 9:1) migration was observed for the less-substituted carbon. However, there are no obvious steric differences in the two potentially migrating carbons of bicyclo[3.2.1]octanoid (**5**), leaving open the question of what forces are responsible for the modest but systematic regioselectivity of its reactions with hydroxyalkyl azides. Assuming antiperiplanar migration relative to the N_2 leaving group, two mechanistic scenarios arising from the intermediate oxonium ion are possible (Figure 3). Thus, addition of azide can occur from either face of the oxonium

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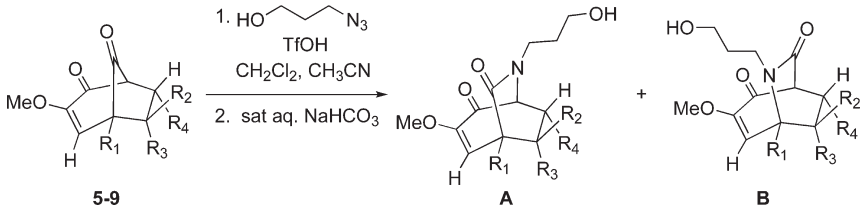
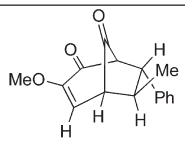
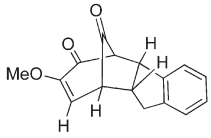
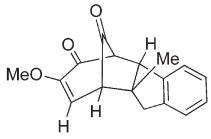
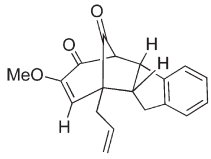
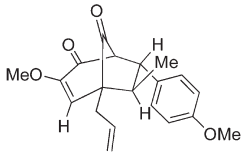
(14) Acids tested in the azido-Schmidt reaction with substrate **6** include $Sc(OTf)_3$, $La(OTf)_3$, $Zn(OTf)_3$, $Yb(OTf)_3/PhCO_2H$, $La(OTf)_3/PhCO_2H$, $Zn(OTf)_3/PhCO_2H$, pTSA, CSA(+), TFA, $BF_3{\cdot}OEt_2$, HBF_4, Tf_2NH, TMSOTf, and TfOH.

TABLE 1. Survey of Bicyclo[3.2.1]octanoids as Azido-Schmidt Substrates



entry	substrate	R_1	bicyclo[3.2.1]octanoid	yield (%)[a]	A:B ratio[b]
1	**5**	H		88	3:1
2	**6**	H		49	2:1
3	**7**	H		40	2:1
4	**8**	allyl		–	–
5	**9**	allyl		–	–

[a]Isolated yield of regioisomeric mixture. [b]Regioisomeric ratio estimated by crude ^{1}H NMR.

ion species (paths a and b as depicted), in each case leading to a mixture of *N*-diazoniumoxazinane intermediates. We speculate that path a should be favored in this case as a result of the presence of potentially interfering steric interaction with the methyl group in path b. Previous work suggests that azide adducts formed in this way can equilibrate *via* chair−chair interconversion prior to loss of nitrogen gas and formation of the iminium ether,[13] at which point the reaction is complete and regiochemistry fully established. Given the relatively low energy differences leading to **14a** over **14b** and lack of obvious preference between the two chair forms of the oxazinanes shown to the left of the diagram in Figure 3, it would be imprudent to speculate further on the cause of the preference for **14a**.

The suitability of these multifunctional iminium ethers for ring-opening screens was validated by treatment of **14** with nucleophilic reagents previously shown to react with simple iminium ethers (Table 3). Products resulting from reactions at both the cationic center (path a) and the *O*-alkyl portion of the iminium ether (path b) were observed in accordance with previously reported examples.

Iminium ether **19** was also selected for screening and prepared according to our previously reported protocol (Scheme 2).[15] We selected this compound on the basis of its simplicity, similarity to previously studied examples,[3e,15] and the presence of a phenyl substituent, which provided a chromophore to aid in product detection and analysis. As usual, this iminium ether could be subjected to base hydrolysis to afford lactam **20**.

Multidimensional Screening of Iminium Ether Substrates. A multidimensional screen was performed using an automated microfluidic reaction screening platform capable of combining specified reagents in a sequential format.[7] The microfluidics platform consists of a multihead syringe pump, liquid handler, a microreactor, and a UV-triggered fraction collector. The liquid handler systematically injects pulses of

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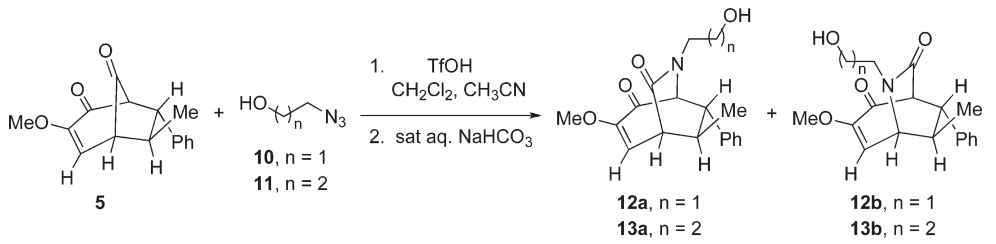
TABLE 2. Optimization of Azido-Schmidt Reaction of Bicyclo[3.2.1]octanoid 5



entry	hydroxyalkyl azide	solvent	temp	ratio (**a**:**b**)[a]
1	**10**	CH_3CN	−20 °C	7.3:1.0
2	**10**	1:1 CH_3CN/CH_2Cl_2	−20 °C	7.6:1.0
3	**10**	CH_2Cl_2	−20 °C	7.6:1.0
4	**10**	CH_3CN	0 °C → rt	6.1:1.0
5	**10**	1:1 CH_3CN/CH_2Cl_2	0 °C → rt	5.8:1.0
6	**10**	CH_2Cl_2	0 °C → rt	4.8:1.0
7	**11**	CH_3CN	−20 °C	2.8:1.0
8	**11**	1:1 CH_3CN/CH_2Cl_2	−20 °C	3.1:1.0
9	**11**	CH_2Cl_2	−20 °C	3.2:1.0
10	**11**	CH_3CN	0 °C → rt	2.4:1.0
11	**11**	1:1 CH_3CN/CH_2Cl_2	0 °C → rt	2.2:1.0
12	**11**	CH_2Cl_2	0 °C → rt	3.1:1.0

[a]Ratios determined by ^{1}H NMR. Only those reactions with full conversion were considered. Yields were not determined.

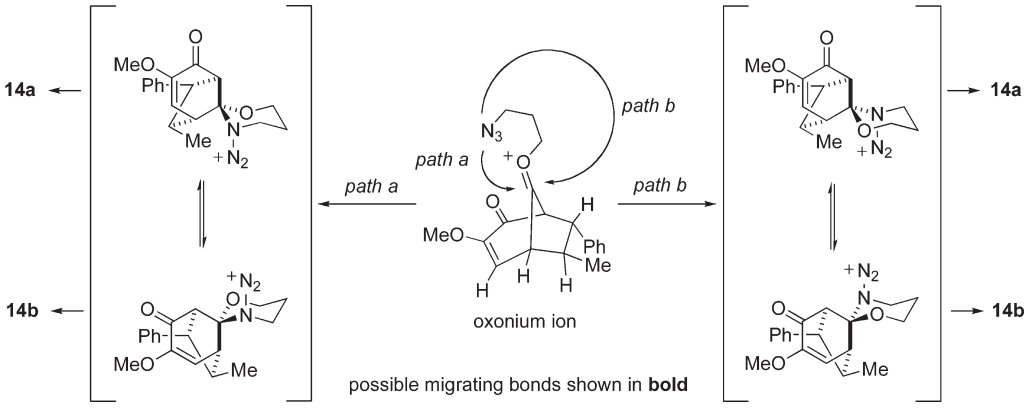
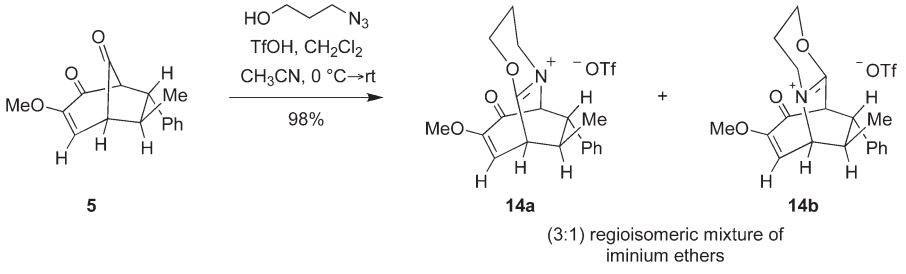


FIGURE 3. Regioselectivity analysis of the azido-Schmidt reaction of **5**.

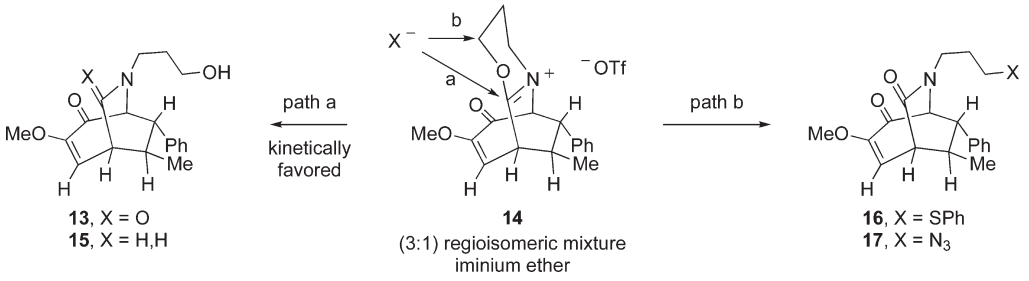
SCHEME 1



reactants into a continuously flowing solvent stream driven by the multihead syringe pump. The three reagent pulses converge in the microreactor and undergo mixing to become a single reaction pulse. The reactions are quenched in the reactor by a continuous flowing stream of water to give each reaction a finite end point. The UV-triggered collection allows for the collection of the most concentrated region of the reaction pulse by setting an acceptable absorbance threshold, thus selectively extracting individual reaction mixtures from the pulse stream.

Using scaffolds **14** and **19**, a total of 23 nucleophilic reaction partners were evaluated (Figure 4). Reaction partners were chosen for their potential to participate in both condensations and cycloadditions. Since there are only a few examples of carbon−carbon bond formations employing reactions of iminium ethers, we focused particular attention

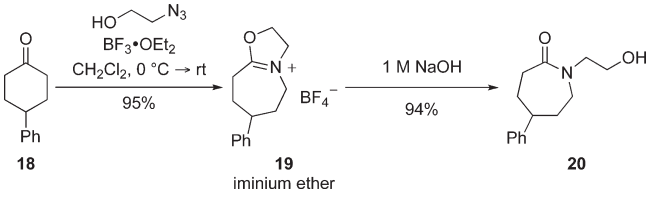
TABLE 3. Heteroatom Nucleophilic Addition Reactions of a Bicyclo[3.2.1]octanoid Derived Iminium Ether



entry	reagent	X	path	product	yield (%)[a]
1	satd aq $NaHCO_3$	O	a	**13**	67
2	$NaBH_4$	H,H	a	**15**	59[b]
3	NaSPh	SPh	b	**16**	62
4	NaN_3	N_3	b	**17**	70

[a]Isolated yield corresponding to major regioisomer. [b]Bicyclo[3.2.2]enone reduced to allylic alcohol.

SCHEME 2



on expansion of these nucleophilic reaction partners. The reactions were screened under neutral conditions as well as in the presence of non-nucleophilic bases, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU, $pK_a = 12$) and *N*,*N*-diisopropylethylamine (DIEA, $pK_a = 9.5$) in order to generate reactive nucleophilic species.

Reactions completed in the microfluidic system were performed using 2 μmol (ca. 1 mg of **14** or 0.6 mg of **19**) of substrate with 3.0 equiv of reaction partner and 3.0 equiv of base (if used). Reagents were prepared as stock solutions in DMSO (ca. 0.25 M for **14** and **19**, 0.75 M for reaction partners and bases) with minimal exposure to air and stored in oven-dried glass sleeves housed in the inert reagent storage block. Each reaction used 8 μL from each desired stock solution for a total reaction volume of 24 μL. Flow rates for the system were set at either 4.5 or 1.2 μL/min to achieve reaction times of 5 or 20 min, respectively. To ensure comparable reaction times for each addition, reactions were quenched by the addition of water (excess) prior to exiting the microreactor. The resulting solutions were analyzed without further treatment using ultra performance liquid chromatography (UPLC)/MS/evaporative light scattering detector (ELSD) analysis.[16]

Previous reports have shown that nucleophilic additions to iminium ethers, such as those attempted within the screen, may require longer reaction times than is possible using the microfluidic apparatus. To ensure that no productive reactions were overlooked on the basis of insufficient reaction time, reactions were also completed under similar conditions in capped glass vials placed in an orbital shaker for 24 h. These reactions were quenched with excess water, transferred to 96-well plates, and analyzed by UPLC/MS/ELSD.

Productive reactions were defined as those affording >20% conversion to a major product according to crude UPLC/MS/ELSD analysis. Positive outcomes were observed with five reaction partners for iminium ether **19** and with 10 reaction partners for iminium ether **14**. These reactions were subsequently scaled up, and the products were isolated and characterized using traditional spectroscopic methods. For comparison purposes, we elected to conduct scale-up reactions of both **14** and **19** with each reaction partner that was found to be productive in the initial screens regardless of which substrate indicated the positive outcome. Additionally, scale-up reactions were carried out in acetonitrile instead of DMSO as solubility of the iminium ether was no longer a primary concern. The change to acetonitrile not only increased the ease of product isolation but also increased the overall yield. DIEA was selected as a base for the scale-up studies, since DBU was found to react with the iminium ether substrates leading to adduct formation.

Products Derived from Reaction Screening and Proposed Mechanisms. All products isolated from the scale-up process were the result of nucleophilic addition to the iminium ether position distal to the nitrogen (Tables 4 and 5) *via* path b (Table 3). The preference for product formation *via* one path over another is dependent upon several factors, including nucleophile size and the nature of the anion-stabilizing group.[15] Since all of the reaction partners used in this study were larger than those previously shown to result in path a products, it is not surprising that we observed a preference for addition to the less hindered site (path b in Table 3). Prior to this study, the use of carbon nucleophiles has been limited to preformed sodium salts of stabilized carbon species. In previous studies, addition of carbon nucleophiles to iminium ethers was shown to proceed through reversible addition *via* path a followed by rapid elimination to afford enamine products.[3d,15] However, this mode of reactivity was not observed here. The feasibility of elimination is dependent upon both the acidity and the steric environment of the α-proton. It is possible that the reaction conditions employed in this screen were not basic enough to induce elimination through this pathway, but this point was not thoroughly examined.

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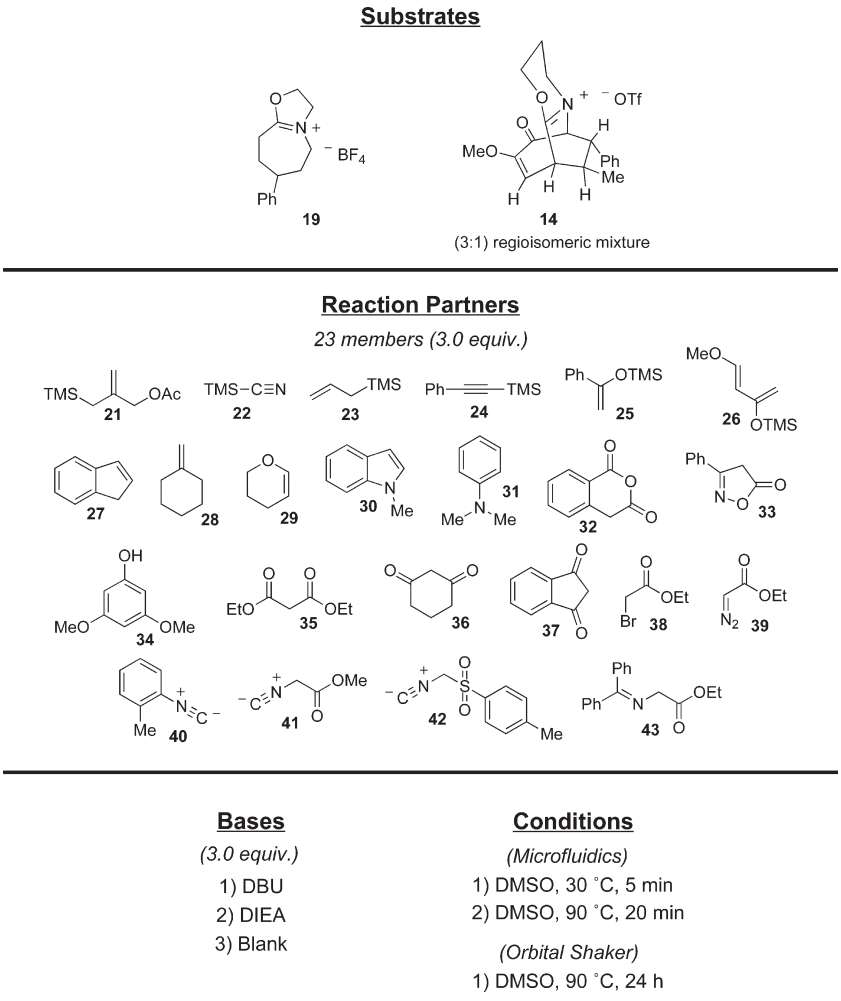


FIGURE 4. Multidimensional screening reaction partners and parameters.

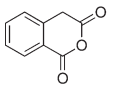
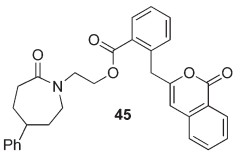
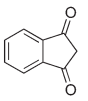
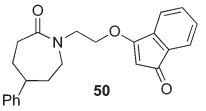
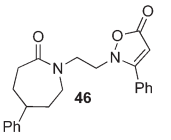
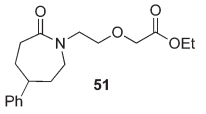
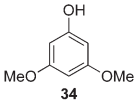
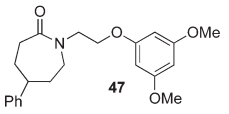
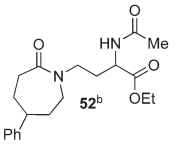
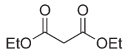
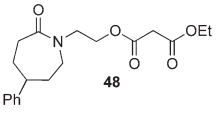
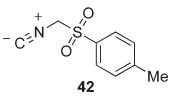
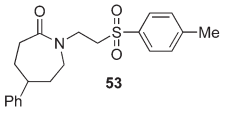
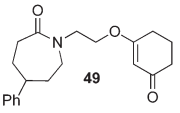
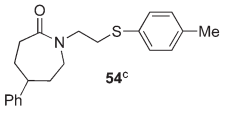
Reaction partners that underwent initial enolate formation frequently favored *O*-alkylation affording compounds **47**, **48**, **49**, and **50** derived from substrate **19**, and compounds **57**, **58**, **59**, and **60** derived from substrate **14**. This mode of addition was noted in previous studies when diethylmalonate sodium salt was used as the nucleophile.[3d,15] Interestingly, the reaction between 3-phenyl-5-isoxazolone (**33**) and substrate **19** gave exclusive *N*-alkylation, whereas the reaction with substrate **14** produced a ca. 1:1 mixture of both *N*-alkylated **56** and *O*-alkylated **57**. This apparent lack of chemoselectivity may be attributed to increased steric interaction between **14** and the 3-phenyl of **33** as compared to the relatively unhindered **19**.

Esters **45** and **55** may also arise from an *O*-alkylation of the iminium ether that is preceded by the pseudodimerization of homophthalic anhydride to first produce acid **63** (Scheme 3). Similar dimerization processes where one or both of the anhydride molecules are replaced by the corresponding free acid have been reported.[17] In addition, approximately equimolar amounts of proposed intermediate **63** and product **45** were isolated when the reaction shown in Scheme 3 was carried out preparatively. Since the process is only catalytic in water, a trace amount of water may be sufficient to initiate the dimerization of the nucleophile. Upon completion, the resulting acid may then open the iminium ether under the basic reaction conditions to provide the observed products. An alternative mechanism may also be possible in which the homophthalic anhydride first opens the iminium ether which may be followed by subsequent dimerization and hydrolysis upon work up. Further mechanistic investigation will be required to differentiate between these two possibilities.

Treatment of the densely functionalized iminium ether **14** with ethyl bromoacetate **38** afforded the ring-opened alkyl bromide **61**. The formation of **61** is most likely a result of bromide addition *via* path b. The formation of bromide anion under the reaction conditions may be attributed to the long reaction times and higher temperatures under which these reactions were completed. Such conditions may induce displacement or elimination of bromide anion, which may then readd to the iminium ether giving the observed bromolactam. Interestingly, when iminium ether **19** was treated with ethyl bromoacetate **38** under the same conditions, the same reactivity was not observed. In this case, the only isolated product was lactam **51**, albeit in low yield. Lactam **51** is likely the product of initial iminium ether hydrolysis followed by displacement of α-halogenated **38**. At this time it

(17) (a) Ayyangar, N. R.; Srinivasan, K. V. *Indian J. Chem., Sect. B* **1983**, *22B*, 1108–1115. (b) Ozcan, S.; Sahin, E.; Balci, M. *Tetrahedron Lett.* **2007**, *48*, 2151–2154. (c) Duddeck, H.; Kaiser, M. *Spectrochim. Acta, Part A* **1985**, *41A*, 913–924.

TABLE 4. Reactions of Iminium Ether 19

entry	reaction partner	product	yield (%)	entry	reaction partner	product	yield (%)
1	 **32**	 **45**	43[a]	6	 **37**	 **50**	25[a]
2	 **33**	 **46**	87[a]	7	 **38**	 **51**	7[a]
3	 **34**	 **47**	29[a]	8	 **39**	 **52**[b]	13[b]
4	 **35**	 **48**	23[a]	9	 **42**	 **53**	40[a]
5	 **36**	 **49**	58[a]	10	 **44**	 **54**[c]	94[c]

[a]Conditions: reaction partner (3.0 equiv), DIEA (3.0 equiv), MeCN, 80 °C, 24 h. [b]Conditions: reaction partner (3.0 equiv), MeCN, 135 °C, 24 h. [c]Conditions: reaction partner (3.0 equiv), KH (3.0 equiv), DMF, 80 °C, 24 h.

is unclear as to why ethyl bromoacetate afforded bromination upon reaction with **14** yet gave little to no reaction with **19**. In this instance, the stabilizing ability of the counterion may also have a notable influence on the reaction. The formation of **19** as a tetrafluoroborate salt imparts greater stability to the complex as compared to the triflate salt of **14**. Attempts made to exchange the triflate anion of **14** for the tetrafluoroborate anion were unsuccessful.

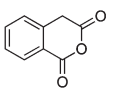
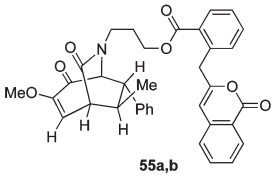
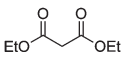
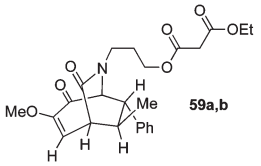
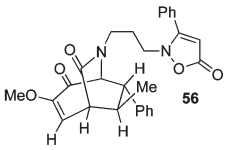
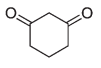
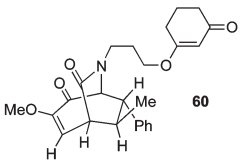
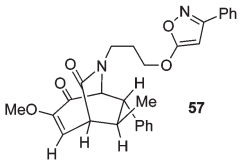
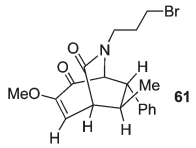
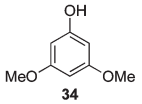
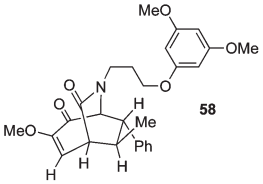
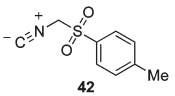
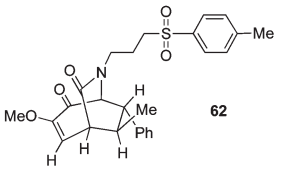
Reactions using isonitrile **42** (TosMIC) afforded lactams **53** and **62** from **19** and **14**, respectively. The structural assignment of **53** was verified by comparison to the same product synthesized using an alternative route (Scheme 4).

TosMIC (**42**) is widely used in the formation of a diverse range of heterocycles.[18] Often in this route *p*-toluenesulfinate **64** serves as a leaving group to enable product aromatization, thereby giving a positive driving force to the overall process. In the absence of an adequate cyclization partner, however, decomposition of TosMIC is known to occur.[19] Early reports proposed that, in TosMIC decomposition, the *p*-toluenesulfinate may be released by direct substitution of the TosMIC anion.[20] More recent studies refute this proposal, suggesting a more complex decomposition route is responsible for *p*-toluenesulfinate release.[19a] Rather than direct substitution, solvent participation[19a] or the self-cyclization of TosMIC may lead to the release of **64** along with a complex mixture of byproducts (Scheme 5). The reactivity and instability of the resulting byproduct make the isolation and identification of these species difficult. Once free in solution, anion **64** can directly add to the electrophilic iminium ethers **19** and **14** to produce sulfones **53** and **62**, respectively. Although the stabilized *p*-toluenesulfinate anion is commonly used in the preparation of sulfones,[19c,20] the reaction of tosyl with an electrophile following ejection from TosMIC to our knowledge has not been reported.

Ethyl diazoacetate (**39**) was the only reaction partner examined that formed a new carbon−carbon bond upon addition to the iminium ether, albeit in low yield. Interestingly, the product isolated from the scale-up reaction did not correspond to the product observed in the original screen. This was apparent as the elucidated structure indicated the incorporation of 1 equiv of acetonitrile that was present only in the scale-up reactions. Attempts to reproduce the original reaction in DMSO were unsuccessful. The proposed mechanism of this transformation involves the initial decomposition of ethyl diazoacetate in the presence of excess acetonitrile to furnish nitrilium ion **65**.[21] Nucleophilic addition of **65** to iminium ether **19** completes the carbon−carbon bond formation to generate amide **52**. Hydrolysis upon

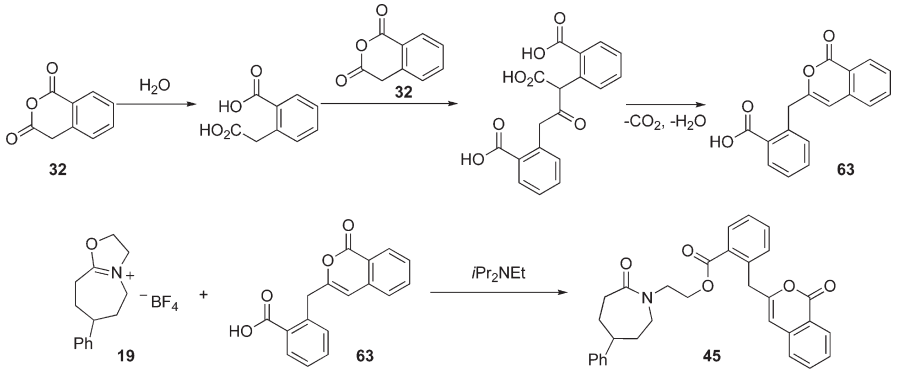
(18) Van Leusen, D.; Van Leusen, A. M. *Org. React.* **2001**, *57*, 417–666.
(19) (a) Van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153–1159. (b) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664–5667. (c) Grigg, R.; Lansdell, M. I.; Thorton-Pett, M. *Tetrahedron* **1999**, *55*, 2025–2044.
(20) Bull, J. R.; Tuinman, A. *Tetrahedron* **1975**, *31*, 2151–2155.
(21) (a) Ibata, T.; Sato, R. *Chem. Lett.* **1978**, *10*, 1129–1130. (b) Doyle, M. P.; Buhro, W. E.; Davidson, J. G.; Elliott, R. C.; Heokstra, J. W.; Oppenhuizen, M. *J. Org. Chem.* **1980**, *45*, 3657–3664. (c) Saegusa, T.; Ito, Y.; Shimizu, T.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3535–3538.

TABLE 5. Reactions of Iminium Ethers 14

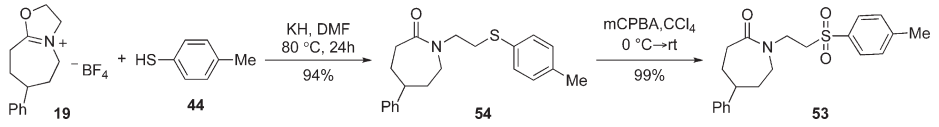
entry	reaction partner	product	yield (%)[a]	entry	reaction partner	product	yield (%)[a]
1	 **32**	 **55a,b**	25[c]	4	 **35**	 **59a,b**	21[c]
2	 **33**	 **56**	26[b]	5	 **36**	 **60**	58[b]
		 **57**	28[b]	6	 **38**	 **61**	64[b]
3	 **34**	 **58**	57[b]	7	 **42**	 **62**	48[b]

[a]Conditions: reaction partner (3.0 equiv), DIEA (3.0 equiv), MeCN, 80 °C, 24 h. [b]Isolated yield corresponding to single major regioisomer. [c]Isolated yield corresponding to a mixture of regioisomers. Only major regioisomer shown.

SCHEME 3



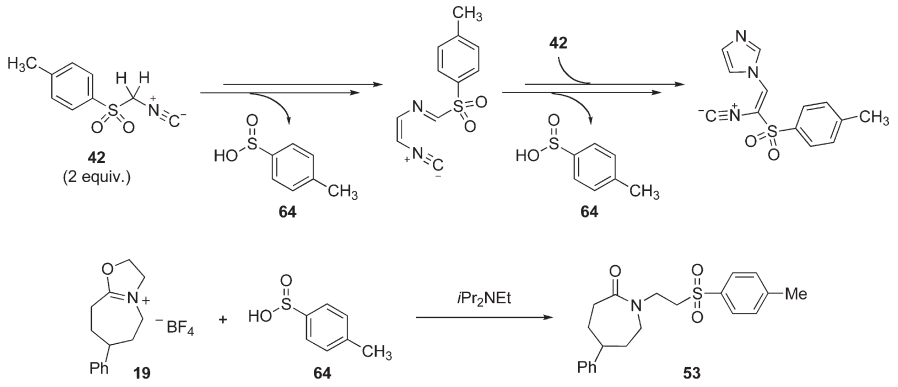
SCHEME 4



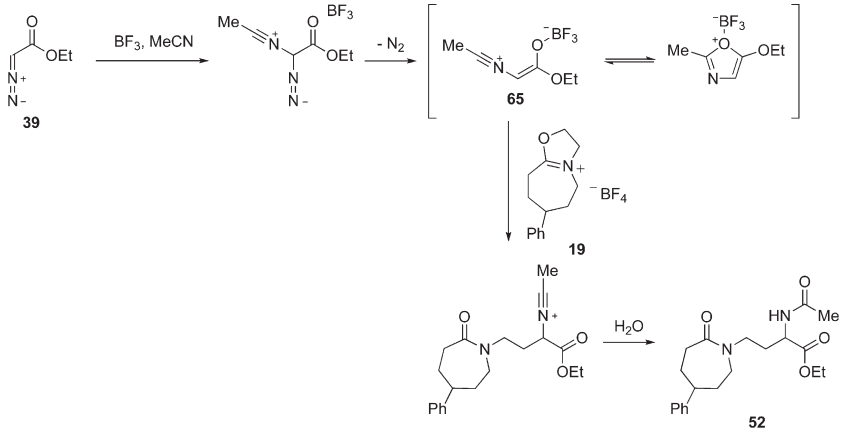
workup provides the observed product, **52** (Scheme 6). It is likely that iminium ether **19** solely participated in this reaction due to the presence of residual BF_3 contaminating substrate **19**, leftover from the initial iminium ether formation which would not have been present in substrate **14** (which used TfOH in iminium ether formation as per Schemes 1 and 2).

Although reaction partners **28** and **41** were also classified as productive in the original reaction screen, the scaled-up reactions afforded complex mixtures from which products could not be identified or isolated. Attempts to improve the reaction by modifying the reaction solvent, time, and temperature were unsuccessful.

SCHEME 5



SCHEME 6



Conclusion

This work exemplifies the ability of microfluidics technology and reaction screening to discover new reactions of polycyclic iminium ethers. The regioselective addition of various carbon nucleophiles was examined under several reaction conditions in an array format to multidimensionally screen the dependent nature of these transformations. Over 400 reactions were completed and analyzed on an analytical scale, resulting in the discovery of both interesting reagent behavior (e.g., homophthalic anhydride pseudodimerization prior to iminium ether addition) and new reaction products (e.g., sulfone formation from reactions with TosMIC). Additional work will focus on the use of the reaction manifolds uncovered in this study for the construction of complex chemical libraries.

Experimental Section

General Procedure for Reaction Screening and Profiling with the Microfluidics System. Stock solutions of iminium ether substrate (0.25 M), reaction partner (0.70 M), and base (0.70 M) were prepared in DMSO and placed in oven-dried glass sleeves that were fitted into a custom-designed 96-well aluminum holding block. The holding block was sealed with a cover containing a continuous flow inert gas chamber and attached to the microfluidics platform. System parameters were set to perform reactions by mixing 8 μL of each reagent at 30 °C for 5 min or at 90 °C for 20 min. The reactions were quenched in the microreactor by flowing water into the quench port. Individual reactions were collected according to a UV trigger into 96-well plates and analyzed by UPLC/MS/ELSD (10−90% CH_3CN), 2 min.

General Procedure for Reaction Screening and Profiling with Orbital Shaker. Stock solutions of substrate (0.25 M), reaction partner (0.70 M), and base (0.70 M) were prepared in DMSO. Individual reactions were prepared in oven-dried glass vials under inert atmosphere by combining 0.50 mL of each stock solution. The glass vials were individually capped and placed in a 96-well holding bock. Reaction blocks were mixed in an orbital mixer for 24 h at 90 °C. The reactions were quenched by the addition of water and analyzed by UPLC/MS/ELSD (10−90% CH_3CN), 2 min.

7-Phenyl-3,5,6,7,8,9-hexahydro-2*H*-oxazolo[3,2-*a*]azepin-4-ium Tetrafluoroborate Salt (19). $BF_3 \cdot OEt_2$ (2.87 mL, 22.9 mmol) was added dropwise over 5 min to a solution of 4-phenyl cyclohexanone (2.00 g, 11.4 mmol) and 2-azido-1-ethanol (1.50 g, 17.2 mmol) in CH_2Cl_2 (60 mL) at 0 °C. Gas evolution appeared upon acid addition. The reaction was warmed to rt, stirred for 12 h, and then evaporated *in vacuo* to yield a colorless oil. The crude oil was purified by silica gel column chromatography (1:9 MeOH−CH_2Cl_2) to afford 3.38 g (97%) of **19** as a white solid. R_f 0.33 (1:9 MeOH−CH_2Cl_2); mp 127.0−128.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 7.35−7.31 (m, 2H), 7.24−7.22 (m, 3H), 4.97−4.86 (m, 2H), 4.28 (app q, J = 10.0 Hz, 1H), 4.16 (app q, J = 10.0 Hz, 1H), 3.88−3.78 (m, 2H), 3.03−2.91 (m, 3H), 2.03−1.83 (m, 4H); ^{13}C NMR (400 MHz, DMSO-d_6) δ_C 179.1, 146.2, 128.5, 126.4 (2), 72.1, 52.4, 46.4, 45.5, 31.4, 27.6, 25.8; IR (neat) 2985, 1739, 1246, 1047 cm^{-1}; MS (ES+) m/z 216.1 (M^+); HRMS calcd for $C_{14}H_{18}NO$ (M^+) 216.1388, found 216.1377.

1-(2-Hydroxyethyl)-5-phenylazepan-2-one (20). A 1 M NaOH solution (1.0 mL) was added to a solution of 7-phenyl-3,5,6,7,8,9-hexahydro-2*H*-oxazolo[3,2-*a*]azepin-4-ium tetrafluoroborate salt (**20**) (100 mg, 0.330 mmol) in CH_2Cl_2 (1 mL), and the biphasic mixture was stirred at rt for 2 h. The reaction was diluted with water (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were combined, washed with brine (10 mL), dried over anhydrous sodium sulfate, and evaporated *in vacuo* to afford 72.4 mg (94%) of **20** as a white solid. R_f 0.43 (1:9 MeOH−CH_2Cl_2); mp 109.5−110.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.29−7.26 (m, 2H), 7.20−7.14 (m, 3H), 3.76−3.63 (m, 5H), 3.51 (dt, J = 13.8, 5.2 Hz, 1H), 3.38 (dd, J = 15.2, 5.6 Hz, 1H), 2.78−2.59 (m, 3H), 2.00−1.97 (m, 2H), 1.74 (q, J = 12.0 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ_C 176.7, 145.9, 128.4, 126.5, 126.4, 61.3, 51.5, 50.1, 48.0, 36.3, 35.8, 30.5; IR (neat) 3428, 1616, 1056, 701 cm^{-1}; MS (ES+) m/z 234.1 (M^+ + 1); HRMS calcd for $C_{14}H_{20}NO_2$ (M^+ + 1) 234.1494, found 234.1452.

General Procedure for the Addition of Nucleophiles to 7-Phenyl-3,5,6,7,8,9-hexahydro-2*H*-oxazolo[3,2-*a*]azepin-4-ium Tetrafluoroborate Salt (45−51 and 53). Diisopropylethylamine (86.0 μL, 0.495 mmol) was added to a solution of homophthalic anhydride (80.1 mg, 0.495 mmol) in anhydrous acetonitrile (1 mL), and the resulting solution was stirred at rt for 5 min. Iminium ether 7-phenyl-3,5,6,7,8,9-hexahydro-2-*H*-oxazolo-[3,2-*a*]azepin-4-ium tetrafluoroborate salt (**19**) (50.0 mg, 0.164 mmol) was added to the solution, and the reaction was heated to 80 °C and stirred for 24 h. After cooling to rt, the crude solution was directly analyzed by LCMS and purified by mass-directed fractionation. Additional purification for characterization (if necessary) was completed by SiO_2 preparative thin layer chromatography (5:95 MeOH−CH_2Cl_2).

2-(2-Oxo-5-phenylazepan-1-yl)ethyl-2-((1-oxo-1*H*-isochromen-3-yl)methyl)benzoate (45). Yellow oil (35.0 mg, 43%); R_f 0.34, (5:95 MeOH−CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.23 (d, J = 8.0 Hz, 1H), 8.03 (dd, J = 8.0, 1.2 Hz, 1H), 7.64 (dt, J = 7.6, 1.6 Hz, 1H), 7.54 (dt, J = 7.6, 1.6 Hz, 1H), 7.46- 7.37 (m, 3H), 7.29−7.26 (m, 3H), 7.21 (m, 1H), 7.20−7.08 (m, 2H), 6.16 (s, 1H), 4.47 (t, J = 5.8 Hz, 2H), 4.33 (s, 2H), 3.88 (m, 1H), 3.78−3.66 (m, 2H), 3.39 (dd, J = 6.2, 1.2 Hz, 1H), 2.72 (tt, J = 12.4, 3.4 Hz, 1H), 2.67−2.61 (m, 2H), 2.01−1.92 (m, 2H), 1.80−1.63 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ_C 175.5, 166.7, 162.7, 156.6, 145.9, 137.5, 137.4, 134.7, 132.6, 132.1, 131.1, 129.4, 129.3, 128.5, 127.7, 127.5, 126.6, 126.5, 125.3, 120.1, 103.9, 62.9, 49.9, 48.1, 47.4, 37.6, 36.4, 36.1, 30.7; IR (neat) 1724, 1652, 1487, 1257, 1134 cm^{-1}; MS (ES+) m/z 496.2 (M^+ + 1); HRMS calcd for $C_{31}H_{30}NO_5$ (M^+ + 1) 496.2124, found 496.2140.

2-(2-(2-Oxo-5-phenylcycloheptyl)ethyl)isoxazole-5(2*H*)-one (46). Synthesized according to the general procedure where 3-phenyl-5-isoxazolone (79.7 mg, 0.495 mmol) was substituted for homophthalic anhydride. Clear oil (47.5 mg, 87%); R_f 0.41, (5:95 MeOH−CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.54−7.42 (m, 5H), 7.27−7.24 (m, 2H), 7.17 (m, 1H), 7.12−7.10 (m, 2H), 5.44 (s, 1H), 3.90−3.79 (m, 2H), 3.73−3.60 (m, 2H), 3.48 (m, 1H), 3.33 (dd, J = 15.1, 5.4 Hz, 1H), 2.71 (tt, J = 12.0, 3.6 Hz, 1H), 2.54 (m, 2H), 1.97 (m, 2H), 1.73−1.62 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ_C 175.4, 170.5, 169.2, 145.7, 131.7, 129.3, 128.5, 127.5, 126.9, 126.5, 126.4, 90.9, 51.8, 50.8, 47.9, 47.1, 36.3, 35.9, 30.5; IR (neat) 2927, 1737, 1643, 1490, 1450, 761, 700 cm^{-1}; MS (ES+) m/z 377.1 (M^+ + 1); HRMS calcd for $C_{23}H_{25}N_2O_3$ (M^+ + 1) 377.1865, found 377.1827.

(*E*)-6-(3-Hydroxypropyl)-3-methoxy-8-methyl-9-phenyl-6-azabicyclo[3.2.2]non-2-ene-4,7-dione (13a) and (*E*)-6-(3-Hydroxypropyl)-3-methoxy-9-methyl-8-phenyl-6-azabicyclo[3.2.2]non-3-ene-2,7-dione (13b). Saturated aqueous $NaHCO_3$ solution (5 mL) was added to a solution of polycyclic iminium ether **14** (100 mg, 2.17 mmol) in CH_2Cl_2 (5 mL), and the biphasic mixture was stirred at rt for 2 h. The reaction was diluted with water (5 mL) and was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to give a yellow oil. The crude material was purified by SiO_2 preparative thin layer chromatography (5:95 MeOH−CH_2Cl_2) to afford 33.1 mg (67%) of **13a** and 11.0 mg (22%) of **13b** as a yellow oils. Characterization data for **13a**: R_f 0.76 (1:9 MeOH−CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.31−7.22 (m, 3H), 7.10−7.07 (m, 2H), 6.34 (d, J = 10.4 Hz, 1H), 4.10 (d, J = 5.6 Hz, 1H), 3.69 (s, 3H), 3.66−3.47 (m, 4H), 3.33 (dd, J = 10.0, 1.2 Hz, 1H), 3.10 (t, J = 6.0 Hz, 1H), 2.61 (t, J = 6.8 Hz, 1H), 1.68 (m, 2H), 1.22 (d, J = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ_C 188.9, 172.9, 153.3, 137.4, 129.0, 128.3, 127.9, 116.9, 73.0, 58.3, 55.5, 52.7, 48.9, 43.4, 41.2, 30.5, 22.9; IR (neat) 3421, 2958, 1650, 1623, 1456, 1126 cm^{-1}; MS (ES+) m/z 330.1 (M^+ + 1); HRMS calcd for $C_{19}H_{24}NO_4$ (M^+ + 1): 330.1705, found 330.1548. Characterization data for **13b**: (R_f 0.72 (1:9 MeOH−CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30−7.21 (m, 3H), 7.04−7.02 (m, 2H), 6.37 (d, J = 9.2 Hz, 1H), 3.95 (d, J = 4.8 Hz, 1H), 3.89 (dd, J = 9.2, 0.8 Hz, 1H), 3.82 (m, 1H), 3.67 (s, 3H), 3.59 (m, 1H), 3.51−3.41 (m, 2H), 3.24 (m, 1H), 2.98 (dd, J = 6.4, 4.8 Hz, 1H), 2.64 (pent, J = 6.8 Hz, 1H), 1.82−1.70 (m, 2H), 1.23 (d, J = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ_C 186.3, 169.5, 154.9, 138.4, 129.0, 128.0, 127.7, 118.2, 67.9, 59.7, 58.1, 55.5, 48.2, 44.4, 42.7, 30.6, 21.5; IR (neat) 3421, 2960, 1681, 1649, 1457, 1124 cm^{-1}; MS (ES+) m/z 330.1 (M^+ + 1); HRMS calcd for $C_{19}H_{24}NO_4$ (M^+ + 1) 330.1705, found 330.1538.

Synthesis of Polycyclic Iminium Ether Mixture (14a,b). To a solution of racemic 3-methoxy-6-methyl-7-phenylbicyclo-[3.2.1]oct-3-ene-2,8-dione (300 mg, 1.17 mmol) and 3-azido-1-propanol (118 mg, 1.17 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added a 1.17 M stock solution of TfOH (3.11 mL, 3.51 mmol) dropwise over 5 min. The acid stock solution was freshly prepared by the addition of TfOH (0.40 mL, 4.51 mmol) to a mixture of CH_3CN (0.7 mL) and CH_2Cl_2 (2.9 mL). After 1 h at 0 °C the reaction was warmed to rt and stirred for 12 h. Upon dilution with water (10 mL) the solution was extracted with CH_2Cl_2 (3 × 20 mL), and the organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to afford 527 mg (98%) of **14a,b** as a fluffy yellow solid and a mixture of regioisomers (3.5:1.0 regioisomeric ratio determined by ^{1}NMR). Mp 88.5−91.0 °C; ^{1}NMR (400 MHz, $CDCl_3$) δ_H 7.32−7.19 (m, 3.9H), 7.15−7.13 (m, 2H), 7.07−7.05 (m, 0.6H), 6.70 (d, J = 9.0 Hz, 0.3H), 6.38 (d, J = 10.0 Hz, 1H), 4.94−4.85 (m, 1.3H), 4.78−4.72 (m, 1.3H), 4.66 (m, 0.3H), 4.45, (d, J = 5.0 Hz, 1H), 4.31 (m, 1H), 4.12−4.06 (m, 0.6H), 3.89 (m, 0.3H), 3.80 (m, 1H), 3.70 (s, 3H), 3.69 (s, 0.9H), 3.64 (d, J = 11.0 Hz, 1H), 3.61 (m, 1H), 3.43 (m, 0.3H), 2.80−2.74 (m, 1.3H), 2.43−2.39 (m, 1.3H), 2.30−2.16 (m, 1.3H), 1.30 (d, J = 7.0 Hz, 0.9H), 1.25 (d, J = 7.0 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ_C 183.7, 181.3*, 177.4, 171.9*, 154.2*, 153.1, 135.9*, 135.0, 129.2*, 129.1, 128.7, 128.4, 128.3*, 127.3*, 117.2*, 114.1, 76.3, 71.0, 70.8*, 64.8*, 63.0*, 55.9*, 55.8, 48.8, 47.6*, 46.7, 46.5*, 45.1, 42.0, 41.9*, 21.5, 20.5*, 19.7, 19.7*; IR (neat) 3055, 1700, 1662, 1265, 1031, 738, 703, 639 cm^{-1}; MS (ES+) m/z 312.1 (M^+); HRMS calcd for $C_{19}H_{22}NO_3$ (M^+) 312.1600, found 312.1582.

(*E*)-3-Methoxy-8-methyl-9-phenyl-6-(3-(phenylthio)propyl)-6-azabicyclo[3.2.2]non-2-ene-4,7-dione (16). To a solution of potassium hydride (13.0 mg, 0.325 mmol) in anhydrous DMF (0.5 mL) was added a solution of benzenethiol (33.0 μL, 0.325 mmol) in anhydrous DMF (0.5 mL). The mixture was stirred at rt for 5 min, and bicyclic iminium ether **19** was added to the flask. The reaction mixture was stirred at 80 °C for 24 h. After cooling, the solution was diluted with water and extracted with

diethyl ether (3 × 10 mL). The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to give a yellow oil. The crude material was purified by SiO_2 preparative thin layer chromatography (3:2 EtOAc−Hex) to afford 21.2 mg (62% based on the major regioisomer in reactant) of **16** as a yellow oil. R_f 0.46 (3:2 EtOAc−Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.35−7.17 (m, 8H), 7.05−7.02 (m, 2H), 6.32 (d, J = 10.4 Hz, 1H), 4.07 (d, J = 5.6 Hz, 1H), 3.67 (s, 3H), 3.53 (t, J = 6.8 Hz, 2H), 3.30 (dd, J = 10.0, 1.2 Hz, 1H), 3.04 (t, J = 6.2 Hz, 1H), 2.88 (t, J = 7.2 Hz, 2H), 2.57 (pent, J = 6.8 Hz, 1H), 1.84 (pent, J = 7.2 Hz, 2H), 1.20 (d, J = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ_C 189.1, 171.4, 153.3, 137.6, 135.7, 129.8, 129.1, 129.0, 128.4, 127.8, 126.3, 116.9, 72.8, 55.4, 52.9, 49.3, 45.9, 41.1, 31.3, 27.8, 22.9; IR (neat) 2923, 1672, 1620, 1456, 1126, 700 cm^{-1}; MS (ES+) m/z 422.1 (M^+ + 1); HRMS calcd for $C_{25}H_{28}NO_3S$ (M^+ + 1) 422.1790, found 422.1785.

General Procedure for the Addition of Nucleophiles to Polycyclic Iminium Ether Triflate Salt (55−62). Diisopropylethylamine (112.0 μL, 0.650 mmol) was added to a solution of homophthalic anhydride (105 mg, 0.650 mmol) in anhydrous acetonitrile (2 mL), and the resulting solution was stirred at rt for 5 min. Polycyclic iminium ether **14** (100.0 mg, 0.216 mmol) was added to the solution, and the reaction was heated to 80 °C and stirred for 24 h. After cooling to rt, the crude solution was directly analyzed by LCMS and purified by mass-directed fractionation. Additional purification for characterization (if necessary) was completed by SiO_2 preparative thin layer chromatography (5:95 MeOH−CH_2Cl_2). Alternatively, some reactions were similarly completed on a 0.216 mmol scale using proportional amounts of the necessary reagents.

(*E*)-3-(3-Methoxy-8-methyl-4,7-dioxo-9-phenyl-6-azabicyclo-[3.2.2]non2-en-6-yl)propyl 2-((1-oxo-1*H*-isochromen-3-yl)methyl)-benzoate (55a) and (*E*)-3-(3-Methoxy-9-methyl-2,7-dioxo-8-phenyl-6-azabicyclo[3.2.2]non-3-en-6-yl)propyl-2-((1-oxo-1*H*-isochromen-3-yl)mehtyl)benzoate (55b). Clear oil (32.6 mg, 25% as an inseparable mixture of regioisomers); R_f 0.25 (3/2 EtOAc−Hex); ^{1}NMR (400 MHz, $CDCl_3$; regioisomers indicated by asterisks) δ_H 8.21 (dd, J = 8.0, 0.4 Hz, 1H), 8.02 (dd, J = 8.0, 1.2 Hz, 1H), 7.61 (dt, J = 7.6, 1.2 Hz, 1H), 7.51 (dt, J = 7.6, 1.2 Hz, 1H), 7.43−7.36 (m, 3H), 7.29−7.21 (m, 4H), 7.10 (m, 2H), 7.02* (m, 0.46), 6.42* (d, J = 9.2 Hz, 0.23H) 6.33 (d, J = 10.4 Hz, 1H), 6.11 (s, 1H), 6.09* (s, 0.23H), 4.29 (s, 2H), 4.32−4.21 (m, 2H), 4.11 (d, J = 5.6 Hz, 1H), 3.91* (d, J = 4.80 Hz, 0.23H), 3.88* (m, 0.23H), 3.77* (m, 0.23H), 3.68 (s, 3H), 3.65* (s, 0.69H), 3.63 (m, 1H), 3.51 (m, 1H), 3.38* (m, 0.23H), 3.29 (dd, J = 10.0, 1.2 Hz, 1H), 3.15 (t, J = 6.4 Hz, 1H), 2.94* (t, J = 5.4 Hz, 0.23H), 2.58 (p, J = 6.8 Hz, 1H), 2.03−1.89 (m, 2H), 1.20 (d, J = 7.2 Hz, 3H), 1.18* (d, J = 6.8 Hz, 0.69H); ^{13}C NMR (400 MHz, $CDCl_3$) δ_C 189.2, 186.6*, 171.3, 169.4*, 166.9*, 166.8, 162.7, 160.5*, 156.8, 153.3, 152.2*, 138.6*, 138.9*, 137.3, 137.4, 137.2, 136.9*, 134.8*, 134.6, 132.3*, 132.5, 132.0*, 131.9, 131.2, 129.6, 129.4, 129.3*, 129.0, 128.9*, 128.4, 128.0*, 127.8*, 127.7, 127.6, 127.5*, 127.4, 125.3*, 125.3, 120.0, 118.6*, 117.5*, 117.0, 103.8, 103.8*, 72.7, 68.2*, 62.6*, 62.0, 59.4*, 55.4, 55.4*, 52.7, 49.2, 48.1*, 44.9*, 43.7, 42.7*, 41.2, 37.8*, 37.6, 27.7*, 27.4, 22.9, 21.4*; IR (neat) 1720, 1670, 1622, 1456, 1259, 1130, 730 cm^{-1}; MS (ES+) m/z 592.2 (M^+ + 1); HRMS calcd for $C_{36}H_{34}NO_7$ (M^+ + 1) 592.2335, found 592.2310.

(*E*)-3-Methoxy-8-methyl-6-(3-(3-oxocyclohex-1-enyloxy)-propyl)-9-phenyl-6-azabicyclo[3.2.2]non-2-ene-4,7-dione (60). Synthesized according to the general procedure where 1,3-cyclohexadione (36.4 mg, 0.325 mmol) was substituted for homophthalic anhydride. Clear oil (21.6 mg, 63% based on the major regioisomer in reactant); R_f 0.42 (5:95 MeOH−CH_2Cl_2); ^{1}NMR (400 MHz, $CDCl_3$) δ_H 7.31−7.24 (m, 3H), 7.09−7.06 (m, 2H), 6.33 (d, J = 10 Hz, 1H), 5.29, (s, 1H), 4.08 (d, J = 5.2 Hz, 1H), 3.77 (t, J = 6.0 Hz, 2H), 3.68 (s, 3H), 3.74 (m, 1H), 3.44 (m, 1H), 3.30 (dd, J = 10.0, 1.2 Hz, 1H), 3.08 (t, J = 6.0 Hz, 1H), 2.58 (t, J = 6.8 Hz, 1H), 2.39 (t, J = 6.4 Hz, 2H), 2.33 (t, J = 6.4 Hz, 2H), 1.94 (m, 4H), 1.20 (d, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ_C 199.7, 189.2, 177.6, 171.3, 153.2, 137.6, 129.0, 128.3, 127.8, 117.0, 102.9, 73.0, 65.3, 55.5, 52.9, 49.2, 43.9. 41.2, 36.7, 28.8, 27.3, 22.8, 21.1; IR (neat) 1643, 1600, 1218, 1184 cm^{-1}; MS (ES+) m/z 424.2 (M^+ + 1); HRMS calcd for $C_{25}H_{30}NO_5$ (M^+ + 1) 424.2124, found 424.2112.

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Supporting Information Available: Additional experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.