Oxidative nitrogen insertion into silyl enol ether C=C bonds

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ABSTRACT: Here we demonstrate a fundamentally new reactivity of the silyl enol ether functionality utilizing an *in situ*-generated "iodonitrene"-like species. The present transformation inserts a single nitrogen atom between the silyl enol ether olefinic carbons with concomitant cleavage of the C=C bond without fragmentation. Overall, this facile transformation converts a *C*-nucleophilic silyl enol ether to the corresponding *C*-electrophilic *N*-acyl-*N*,*O*-acetal. This unprecedented access to α-amidoalkylating agents enables facile and modular derivatization, allowing deep exploration of unchartered chemical space. Applications presented herein include late-stage nitrogen insertion into carbon skeletons of complex natural products with previously unattainable regioselectivity, as well as modified conditions for ^{15}N labeling of amides and lactams.

INTRODUCTION

In recent years, synthetic methods for the incorporation of nitrogen into organic compounds have experienced a renaissance, with the development of many fundamentally new reactivity concepts and selectivity paradigms.[1–3] Among these, nitrogen incorporation methods with concomitant reorganization of a carbon skeleton are a particularly interesting class of transformations. Reshuffling C-C bond connectivity in the course of nitrogen incorporation has many advantages, including the ability to access functional group-rich arrays or skeletal architecture that may be difficult to obtain by other means[4–6] or the ability to achieve late-stage skeletal diversification of natural products or drug candidates.[7–9]

Of particular interest are electrophilic ammonia surrogates, which allow nitrogen incorporation without requirement for specific substituents. Within this area of investigation, ammonium salts in the presence of an iodine(III) reagent have shown considerable promise[10] since their first report in 2016 for the oxidative amination of sulfoxide to sulfoximines (see **Figure 1A**, panel 1).[11] The reactivity diversity possible with this reagent combination is exemplified by the variety of oxidation modes observed, including formal two-electron,[11] four-electron,[4–9,12–14] and six-electron oxidations (vide infra). Under the reaction conditions, ammonia and $PhI(OAc)_2$ are proposed to give an "iodonitrene"-like species that serves as the active aminating agent.[13]

In the course of our own recent studies of ammonium/iodine(III) oxidations of electron-rich functional groups,[15] we became intrigued by the potential for enol ethers to serve as nucleophilic reaction partners that might fragment or rearrange by means of an nitrene-like intermediate. Successful implementation of this strategy would allow manipulation of aliphatic ketone carbon skeletal structure upon silyl enol ether formation and subsequent ammonium/iodine(III) oxidative rearrangement. Recent reports of related transformations of cyclic (hetero)aromatic nucleophiles (see **Figure 1A**, panel 2) provide important precedent for the potential power of this approach.[7–9] However, the chemistry of acyclic and aliphatic substrates for skeletal rearrangement upon nitrogen incorporation remains largely unexplored. In this work, we describe oxidative C=C cleavage of cyclic and acyclic silyl enol ethers using a combination of ammonium salt and iodine(III) reagent, affording *N*-acyl-*N*,*O*-acetals (see **Figure 1B**).

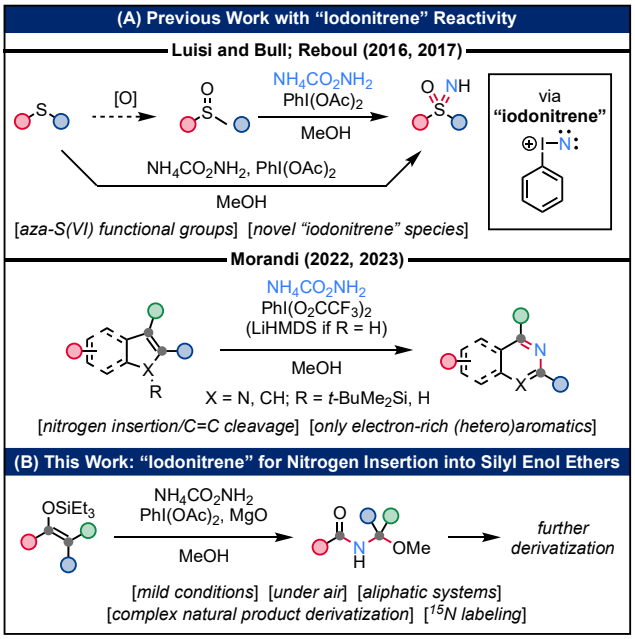


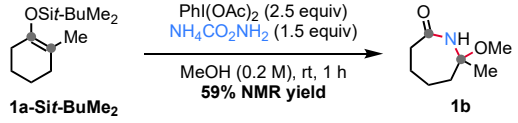
Figure 1. (A) Selected synthetic applications of newly developed "iodonitrene" chemistry. (B) This work: leveraging "iodonitrene" chemistry for oxidative nitrogen insertion into silyl enol ethers derived from aliphatic systems.

RESUTS AND DISCCUSION

We first began our exploration by subjecting silyl enol ether **1a-Si*t*-BuMe2** to $PhI(OAc)_2$ (2.5 equiv) and NH_2COONH_4 (1.5 equiv) in MeOH (see **Figure 2A**). Gratifyingly, the *N*-acyl-*N*,*O*-acetal product **1b** was obtained in 59% NMR yield. The formation of this product represents a formal four-electron oxidation of the silyl enol ether, in line with reported "iodonitrene" reactivity.[10] With our hypothesis validated, we commenced optimization of the reaction conditions. Upon screening through common trialkylsilyl groups, we discovered that the triethylsilyl

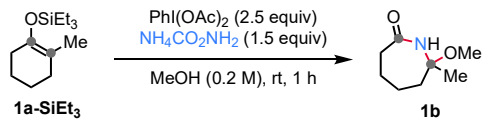
($SiEt_3$) group gave the highest yield (**Figure 2B**, entry 1), presumably due to the optimal balance of steric bulk and stability towards the reaction conditions. All subsequent screening therefore used **1a-SiEt$_3$** as the substrate. Varying the iodine(III) and ammonium sources showed that $PhI(OAc)_2$ and $NH_4CO_2NH_2$ were the optimal reagents, respectively. It is worth noting that other ammonia sources, such as NH_4OAc and $(NH_4)_2CO_3$, gave lower but still preparatively useful yields (entries 4 and 5). Methanol proved to be by far the superior solvent for this transformation, with the yield of **1b** plummeting for larger alcohols (entries 6 and 7) and no detectable product formation with aprotic organic solvents (see SI). When using 2.5 equivalents of $PhI(OAc)_2$, we also detected a significant portion of unreacted starting material. Therefore, the amount of $PhI(OAc)_2$ was increased until full conversion, and maximal yield of **1b** was achieved at 4.0 equivalents (entry 8). The concentration also played a fairly significant role, as decreasing the concentration from 0.2 M to 0.1 M raised the yield to 85% (entry 9). We also explored whether supplementary additives, particularly bases, could further increase the yield. We hypothesized that such additives might serve as an acid scavenger for the released acetic acid over the course of the reaction. Indeed, MgO accomplished this goal by increasing the yield further to 94% (entry 10).

(A) Initial Hit



1a-Si*t*-BuMe$_2$ **1b**

(B) Selected Optimization Results



1a-SiEt$_3$ **1b**

entry	variation from conditions above	% NMR yield [% NMR conversion]
1	none	70 [91]
2	$PhI(O_2CCF_3)_2$ instead of $PhI(OAc)_2$	0 [100]
3	PhI(OH)(OTs) instead of $PhI(OAc)_2$	0 [100]
4	NH_4OAc instead of $NH_4CO_2NH_2$	53 [80]
5	$(NH_4)_2CO_3$ instead of $NH_4CO_2NH_2$	59 [83]
6	EtOH instead of MeOH	43 [81]
7	*i*-PrOH instead of MeOH	5 [54]
8	$PhI(OAc)_2$ (4.0 equiv)	79 [100]
9	$PhI(OAc)_2$ (4.0 equiv) and MeOH (0.1 M)	85 [100]
10	$PhI(OAc)_2$ (4.0 equiv), MgO (2.0 equiv), and MeOH (0.1 M)	94 [100]

Figure 2. (A) Initial hit for the formation of *N*-acyl-*N*,*O*-acetal **1b** under typical "iodonitrene" conditions. (B) Selected results from the subsequent optimization campaign.

With optimal conditions in hand, we next investigated the scope of the nitrogen insertion reaction on silyl enol ethers derived from cyclic and bicyclic ketones (see **Figure 3**). The oxidative nitrogen insertion was first tested on the model substrate **1a** at 0.5 mmol scale, giving the expected product **1b** in 90% isolated yield. The reaction was then rerun at 15 mmol scale, whereupon the yield had only decreased to 76%, indicating the reaction is amenable to significant scale-up. The reaction also proceeded smoothly with the triethylsilyl enol ethers of unsubstituted five, six, seven, eight, and twelve-membered cycloalkanones, giving the corresponding six, seven, eight, nine, and thirteen-membered cyclic *N*-acyl-*N*,*O*-acetals **2b**–**6b** in moderate to good yields, respectively. A phenyl substituent at the ketone α-carbon was also well-tolerated (**7**). The two step silylation/nitrogen insertion sequence was also applied to the commercially available enantioenriched terpenoid (+)-dihydrocarvone giving **8b**. The selective nitrogen insertion into the silyl enol ether C=C bond of **8a** showcases the chemoselectivity of "iodonitrene" for nucleophilic olefins, such as those of the silyl enol ether, over the 1,1-disubstituted olefin of the isopropenyl group. Treatment of **9a** and **10a**, derived from (+)-3-carene and dihydrolevoglucosenone (Cyrene™), respectively, with standard nitrogen insertion conditions gave the bicyclic *N*,*O*-acetals **9b** and **10b**. Attempted double nitrogen insertion into a bis-triethylsilyl enol ether in a bicyclo[2.2.2]octane system **11a** gave only the single nitrogen insertion product **11b**, while the other silyl enol ether hydrolyzed under the reaction conditions.

Upon closer inspection of the initial nitrogen insertion scope, it became clear that the six-membered silyl enol ether **3a** gave a rather poor yield for the oxidative nitrogen insertion (41%), seemingly out of place compared to its five-, seven-, and eight-membered ring congeners (65%, 76%, and 78%, respectively). Though these results initially seemed puzzling, a plausible explanation emerged by considering the innate nucleophilicities of the silyl enol ethers in question. Quantitative nucleophilicities of analogous trimethylsilyl enol ethers were obtained from the Mayr *N* scale, a logarithmic nucleophilicity scale based on the Mayr-Patz equation for predicting bimolecular rate constants of nucleophile/electrophile reactions.[16,17] As displayed in **Figure 4**, the six-membered **3a** has by far the lowest nucleophilicity of the group and correspondingly gives the lowest yield of its *N*,*O*-acetal product **3b**. Additionally, increasing nucleophilicity from **2a** to **4a** to **5a** parallels the increasing trend in yields. We therefore attribute the seemingly aberrant trend of yields for **2b**–**5b** to the innate nucleophilicities of the parent silyl enol ethers.

The scope of the oxidative nitrogen insertion was also explored for triethylsilyl enol ethers derived from aldehydes and acyclic ketones. The linear α-monosubstituted silyl enol ether **12a** gave the expected *N*-formyl-*N*,*O*-acetal product **12b** in relatively poor 28% yield, whereas the α,α-disubstituted **13a** gave **13b** in 64% yield. These yields are likely also related to intrinsic substrate nucleophlicity dictated by substitution pattern. The desired *N*-acyl-*N*,*O*-acetals could also be obtained from a linear dialkyl ketone (**14b**) and alkyl aryl ketone (**15b**). The range of cycloalkyl phenyl ketones with four- to six-membered cycloalkyl rings was also subjected to the silylation/oxidative nitrogen insertion procedure and afforded **16b**, **17b**, and **24b** in good yields. Intriguingly, the cyclobutyl ring of **16** remained intact, with no ring

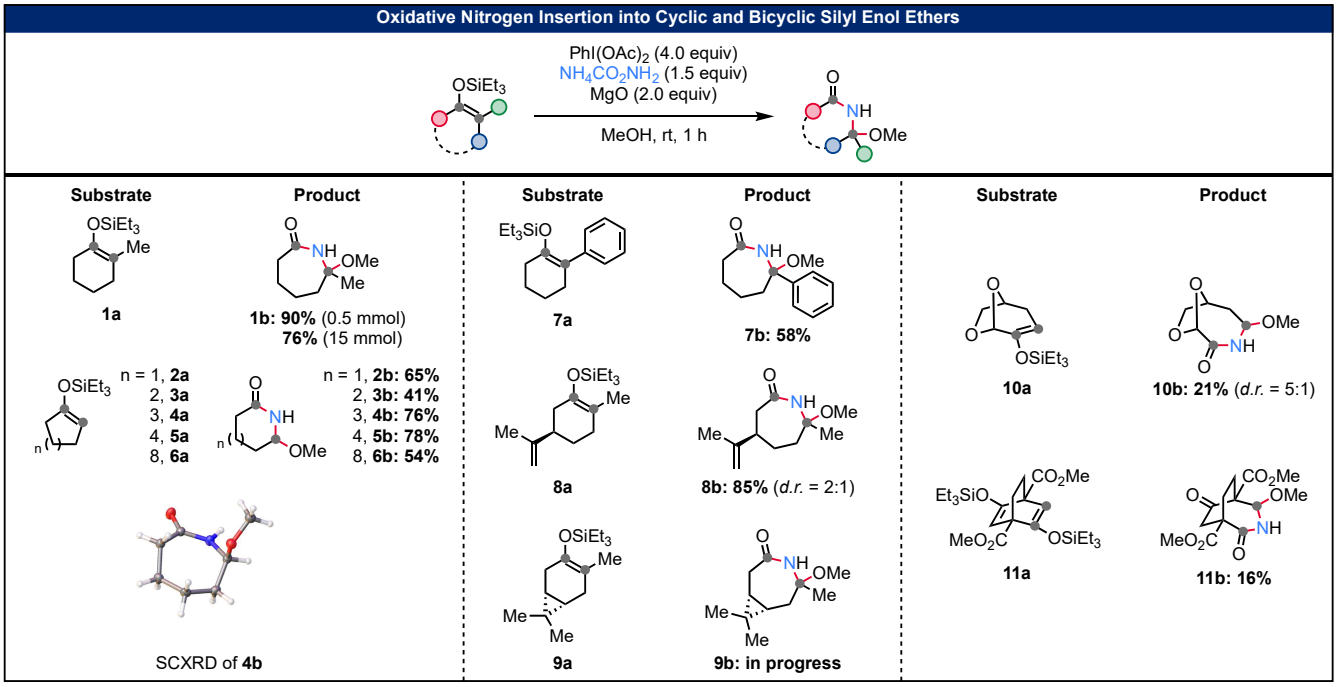


Figure 3. Scope of the oxidative nitrogen insertion into cyclic and bicyclic triethylsilyl enol ethers. All reactions were run at 0.5 mmol scale unless indicated. *3.0 equiv $NH_4CO_2NH_2$, 8.0 equiv $PhI(OAc)_2$, 4.0 equiv MgO

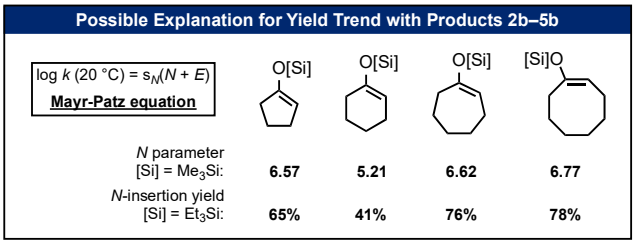


Figure 4. Utilizing Mayr N-parameters to explain the aberrantly low yield of **3b** relative to **2b**, **4b**, and **5b**

expansion products detected. The nitrogen insertion on **16a** was repeated on 4 mmol scale, giving **16b** in 74% yield and further showcasing the scalability of the present reaction. Next, a range of cycloalkyl (hetero)aryl ketones were explored for the functional group tolerance of the present reaction conditions. A range of substituted phenyl rings, including CF_3 (**18**), Br (**19**), vinyl (**20**), Cl/F (**21**), OPh (**25**), and a difluorobenzodioxole (**26**), tolerated the oxidative conditions and afforded the expected products smoothly. In particular, the absence of side reactivity with the styrenyl olefin of **20a** further showcases the chemoselectivity of the "iodonitrene" intermediate. The naphthyl-substituted and β-phenyl enone substrates also gave the desired *N*-acyl-*N*,*O*-acetals (**22b** and **27b**, respectively). Gratifyingly, electron-rich heteroaromatics such as pyrrole (**28**), indole (**23**), furan (**29**), and benzofuran (**30** and **31**) were also well-tolerated under the oxidative conditions. Furthermore, more complex substrates containing an indazole (**32**) and a benzoxazole (**33**) also gave the desired *N*-acyl-*N*,*O*-acetals.

In some cases, *N*-acyl imino ethers were observed as six-electron oxidation products instead of or in addition to the expected *N*-acyl-*N*,*O*-acetals (see **Figure 6**). Silyl enol ethers derived from α-tetralone (**34a**) and tropolone (**35a**) gave imino ethers **34c** and **35c**, respectively. Note that the α-keto group of **35a** spontaneously formed the dimethylacetal under the reaction conditions. When cross-conjugated silyl dienol ether **36a** was exposed to the standard nitrogen insertion conditions, the expected four-electron *N*,*O*-acetal product **36b**, the six-electron imino ether product **36c**, and the eight-electron aromatic azepinone **36d** were all observed. Based on these results, we propose that such overoxidized products form when: 1) the α-carbon is not fully substituted so that a labile hydrogen remains after *N*,*O*-acetal formation and 2) there is a driving force for the formation of the imino ether due to extended conjugation. To the best of our knowledge, this is the first case of six- or eight-electron oxidations being observed under "iodonitrene" conditions.

To showcase the utility of expedient and general access to *N*-acyl-*N*,*O*-acetals, we decided to explore derivatizations harnessing their innate electrophilic nature. In particular, *N*-acyl-*N*,*O*-acetals are air- and moisture-stable sources of *N*-acyl iminium species, which can be generated *in situ* using Brønsted or Lewis acids.[18] Such *N*-acyl iminium species can subsequently be intercepted by a pendent nucleophile.[19] Such reactivity allows for generation of diversity adjacent to amide and lactam nitrogens, a position traditionally difficult to diversify in a modular manner. For our studies, we chose *N*-acyl-*N*,*O*-acetal **1b** for derivatization. Our studies commenced with hydride reduction to give lactam **37** using a combination of silane reductant and silyl triflate Lewis acid. An analogous combination using trimethylsilyl cyanide as the nucleophile gave the α-amido nitrile **38**. Allylation could also be achieved at the *N*,*O*-acetal using a combination of allylmagnesium bromide and $TiCl_4$ to give **39**, presumably proceeding through an elimination-addition sequence via the *N*-acyl imine. A Mukaiyama-Mannich

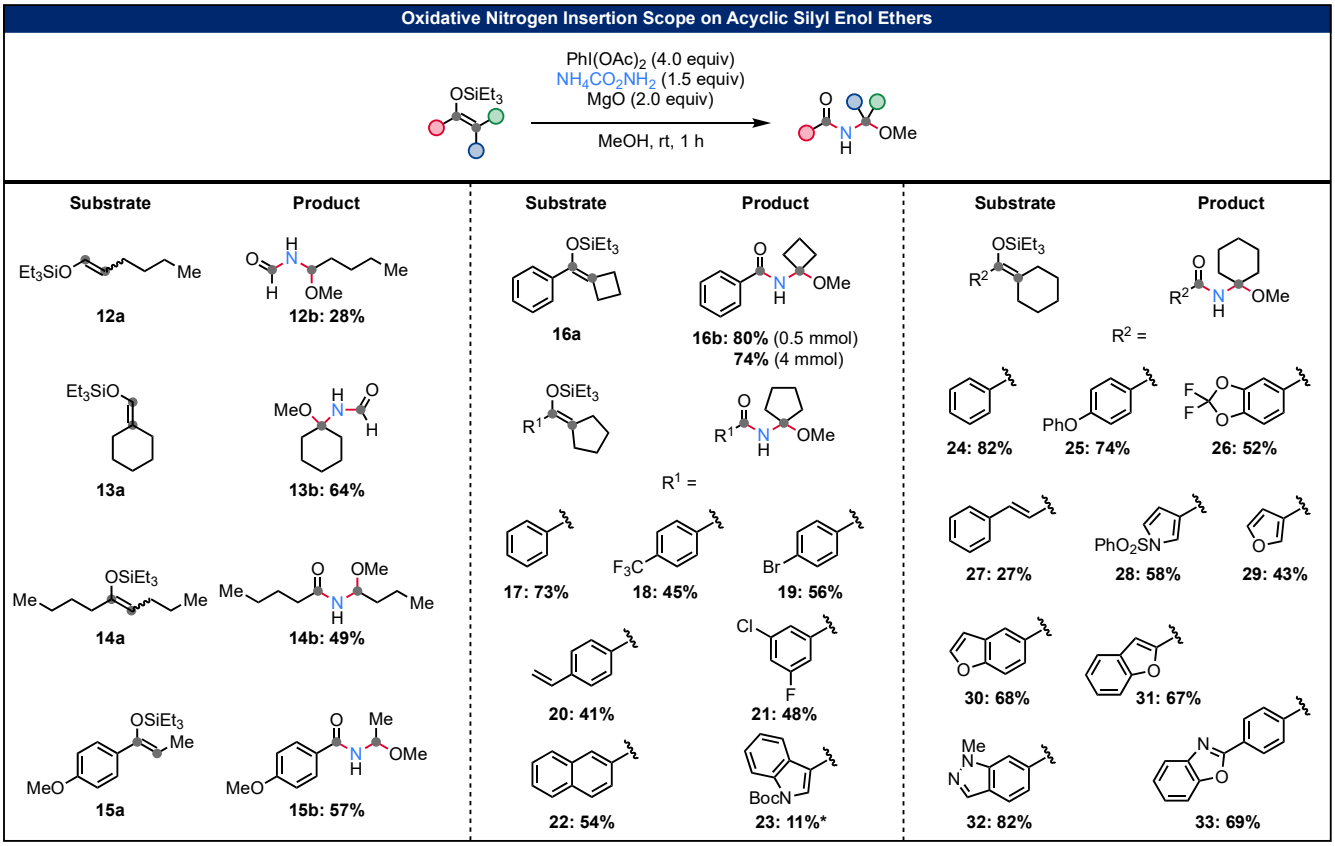


Figure 5. Scope of the oxidative nitrogen insertion into acyclic triethylsilyl enol ethers. All reactions were run at 0.5 mmol scale unless indicated. *2.0 equiv $PhI(OAc)_2$

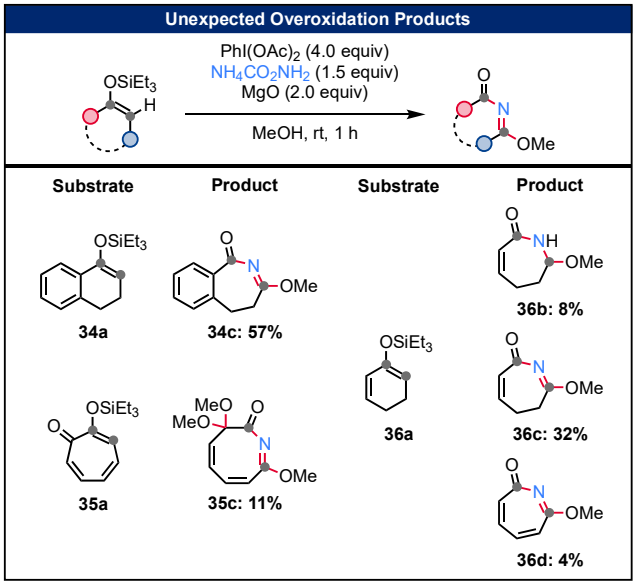


Figure 6. Unexpected overoxidation under standard oxidative nitrogen insertion conditions giving primarily *N*-acyl imino ethers **34c**–**36c** as six-electron oxidation products.

reaction with a silyl ketene acetal was also successful, giving the very sterically hindered array of vicinal quaternary centers of **40** in 48% yield. Under Brønsted acid conditions, the α-amido sulfide **41** was formed. An Arbuzov-type transformation using trimethylphosphite was also successful, giving *N*-methyl-α-amido phosphonate **42** in 27% yield. Lastly, electrophilic aromatic substitution was attempted with *NH*- or *N*-methyl indole. Surprisingly, only the ring-opened, double electrophilic aromatic substitution products **43** and **44** could be isolated, even when the equivalents of indole were lowered. This finding is likely due to the strongly electron-donating nature of the indole ring coupled with the nucleofugal behavior of the lactam under acidic conditions.

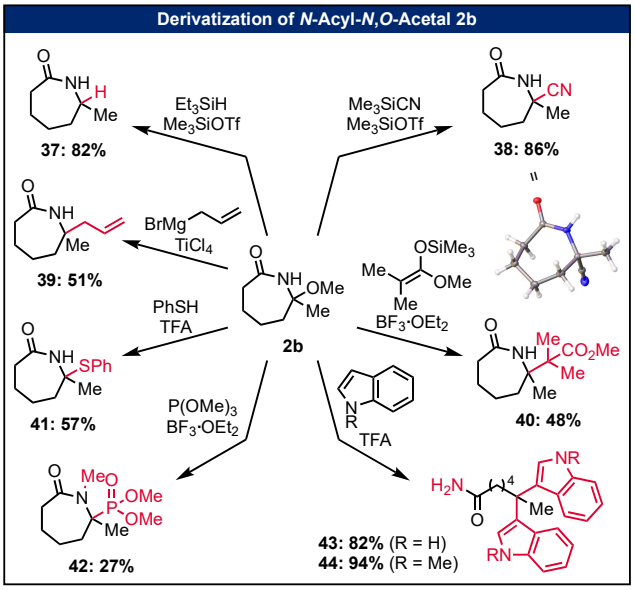


Figure 7. Derivatization of *N*-acyl-*N*,*O*-acetal **2b** showcasing the potential for rapid complexity generation.

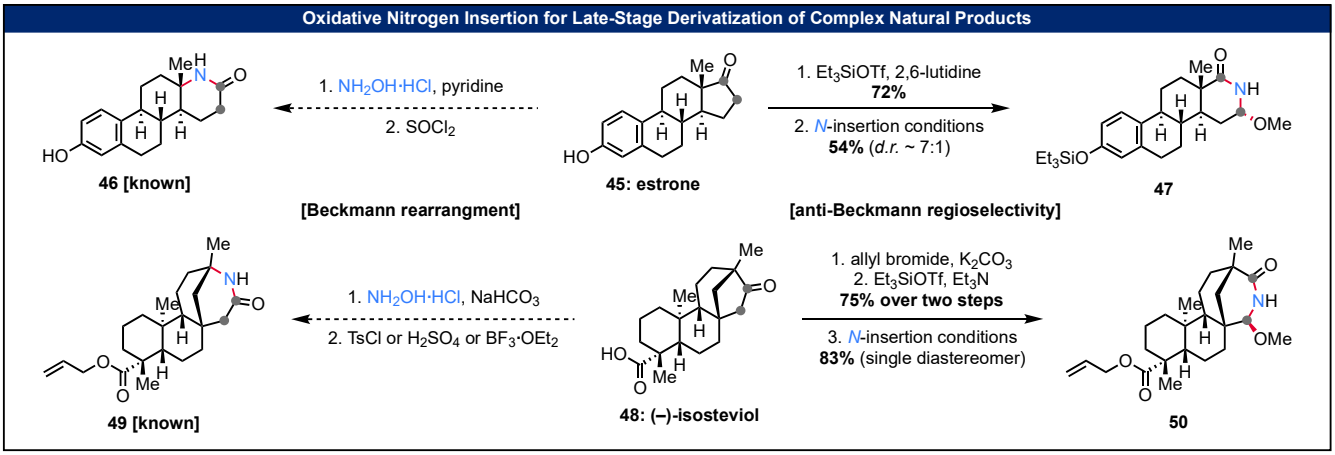


Figure 8. Application of oxidative nitrogen insertion into estrone- and (–)-isosteviol-derived silyl enol ethers **45** and **48**, respectively, with anti-Beckmann regioselectivity. The *N*,*O*-acetals **47** and **50** are primed for further synthetic elaboration.

To further showcase the utility of the present oxidative nitrogen insertion methodology, we considered its utility for single nitrogen atom insertion into the carbon skeletons of complex natural products (see **Figure 8**). The commercially available steroid estrone (**45**) was first doubly silylated with Et_3SiOTf, followed by subjection to standard nitrogen insertion conditions. The expected *N*-acyl-*N*,*O*-acetal **47** was isolated in 54% yield with a ~7:1 *d.r.* The complex terpenoid (–)-isosteviol (**48**), prepared on multigram scale from the alternative sweetener stevioside following a reported procedure, was analogously allyl protected, silylated, and subjected to the standard conditions. The *N*-acyl-*N*,*O*-acetal **50** was isolated in an impressive 83% yield as a single diastereomer. Importantly, these two examples showcase nitrogen insertion into the less substituted side of a ketone, a feat not easily accomplished in most cases. As indicated in **Figure 8**, both estrone and (–)-isosteviol have been transformed into the corresponding ring-expanded lactams **46**[20–22] and **49**[23] using the Beckmann rearrangement. However, in both previously reported instances, only the more substituted fragment was observed to migrate, in accordance with general trends for migratory aptitude. Other existing methods for the conversion of ketones to amides/lactams include the Schmidt reaction, which also generally follows the same regiochemical considerations as the Beckmann rearrangement. In contrast, the present method is not bound by considerations of migratory aptitude as the site of nitrogen insertion is precisely dictated by the regiochemistry of the silyl enol ether. The fact that *N*-acyl-*N*,*O*-acetals are generated instead of amides/lactams is inconsequential as standard redox manipulation can recover the amide/lactam oxidation state (as displayed in **Figure 7**). Furthermore, the *N*,*O*-acetal can be utilized as a new exit vector for further synthetic elaboration. Such operationally simple manipulation of carbon skeletons holds promise for accessing previously hard-to-reach or unreachable areas of chemical space surrounding complex bioactive molecules.

We also envisioned applying the present nitrogen insertion for ^{15}N isotopic labeling of amides and lactams. Like the more familiar ^{1}H and ^{13}C, ^{15}N is a spin 1/2 nucleus and is therefore NMR active, unlike the more abundant quadrupolar ^{14}N. With these favorable magnetic properties and the readily apparent mass shift from ^{14}N, ^{15}N has established a sizeable role in the study of biomolecular structure[24–26] and function,[27–29] MS-based proteomics[30] and metabolomics,[31–33] spin hyperpolarization,[34–36] and mechanistic elucidation.[37,38] However, its low natural abundance (0.4%) and low sensitivity ($\gamma_{15N} \sim 0.10\gamma_{1H}$) almost always necessitate isotopic enrichment to exploit these valuable properties.

Since $^{15}NH_4Cl$ is one of the most common and relatively inexpensive commercially available ^{15}N sources, it was the ideal nitrogen source for the present application. However, unlabeled NH_4Cl performed quite poorly during the initial nitrogen source screen (see SI). Noting that alternative ammonium salts such as $(NH_4)_2CO_3$ performed admirably for the formation of **1b** (**Figure 2**, entry 5), we wondered if it was possible to generate ^{15}N-labeled isotopologues of more active ammonium salts *in situ* using salt metathesis. After a short optimization campaign, we gratifyingly found that the combination of NH_4Cl and Ag_2CO_3 was suitable for generating $(^{15}NH_4)_2CO_3$ with the precipitation of AgCl, giving the desired *N*,*O*-acetal **1b** in decent yield (see SI). Use of these modified conditions with $^{15}NH_4Cl$ afforded **1b-^{15}N** in 83% yield with essentially 100% ^{15}N incorporation, as shown by the absence of the ^{14}NH peak in the ^{1}H NMR spectrum (see **Figure 9**, bottom left spectrum).

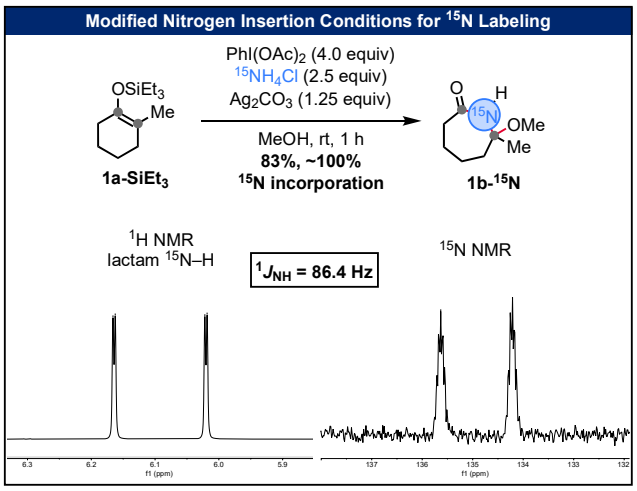


Figure 9. *In situ* generation of $(^{15}NH_4)_2CO_3$ for ^{15}N insertion into **1a-SiEt3**.^{1}H and ^{15}N NMR showing the large $^{1}J_{NH}$ coupling constant in **1b-^{15}N**.

A plausible mechanism of the present transformation is given in **Figure 10**. Previous work on "iodonitrene" chemistry has suggested that the structure of the active aminating agent is **51**, since the corresponding mass was detected by flow HRMS.[13]

This claim has been somewhat contentious, as detection under MS conditions could be due to various fragmentation pathways and does not prove its existence in solution. Accordingly, alternative structures for the "iodonitrene" intermediate have been proposed, such as **52**.[6] Yet another reasonable intermediate is **53**, formed by the iminoiodinane PhI=NH displacing an acetate group on a second equivalent of $PhI(OAc)_2$. Regardless of the true structure of the "iodonitrene" intermediate, the lack of two-electron oxidation products in favor of available four-electron pathways strongly suggests that one equivalent of ammonia must react with two equivalents of the iodine(III) reagent to form the active aminating species,[12] conferring nitrene-like reactivity. Subsequently, the "iodonitrene" undergoes aziridination with the nucleophilic silyl enol ether olefin. The electrofugal nature of the trialkylsilyl group coupled with the nucleofugal nature of the iodonium cause the aziridine C–C bond (formerly silyl enol ether C=C bond) to rupture, giving an *N*-acyl imine species. Finally, incorporation of methanol gives the observed *N*-acyl-*N*,*O*-acetal product.

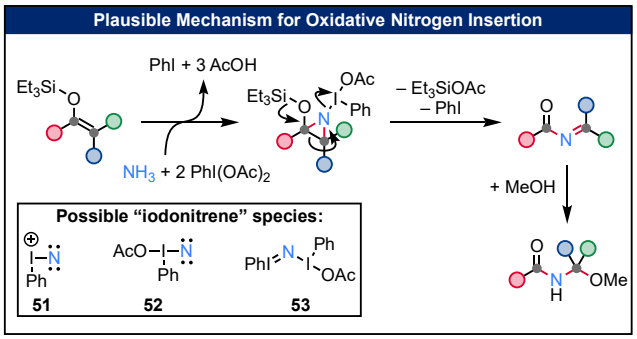


Figure 10. A plausible mechanism for oxidative nitrogen insertion into silyl enol ethers with speculative structures for the "iodonitrene" intermediate.

CONCLUSIONS

We have developed a robust method to perform oxidative insertion of nitrogen into the C=C bond of silyl enol ethers using "iodonitrene" reactivity. The present method exemplifies a fundamentally new mechanistic paradigm in silyl enol ether reactivity, achieving formal four-electron oxidation with reorganization of the carbon skeleton. The efficacy of this transformation has been demonstrated on a wide variety of cyclic, bicyclic, and acyclic silyl enol ethers, giving the corresponding *N*-acyl-*N*,*O*-acetals in generally high yields. This reaction proceeds rapidly under mild conditions without the need for inert atmosphere and shows good tolerance of a wide variety of substituents and heteroatoms. The *N*-acyl-*N*,*O*-acetal products serve as a robust platform for further modular derivatization adjacent to amide and lactam nitrogens, a position traditionally difficult to functionalize. We have also shown the versatility of this transformation in achieving previously inaccessible late-stage skeletal modifications of complex natural products. Furthermore, modified conditions allow near 100% incorporation of ^{15}N into *N*-acyl-*N*,*O*-acetals using readily available $^{15}NH_4Cl$.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures and analytical data (PDF)

Accession Codes

CCDC 2353891 and 2353892 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

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A.L. and S.Y. conceived the idea for this project. S.Y. performed the initial exploratory work. A.L. performed the reaction optimization. A.L., A.G., and S.Y. all contributed to the substrate scope. A.L. performed the *N*,*O*-acetal derivatization and ^{15}N labeling. A.L. wrote the majority of the manuscript with input from all authors. Z.B. and L.K. supervised the project.

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