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Oxidative Nitrogen Insertion into Silyl Enol Ether C═C Bonds

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Cite This: J. Am. Chem. Soc. 2024, 146, 21129−21136
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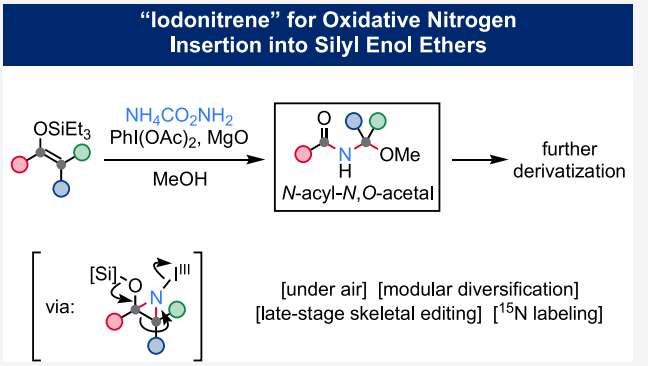
ABSTRACT: Here, we demonstrate a fundamentally new reactivity of the silyl enol ether functionality utilizing an in situ-generated iodonitrene-like species. The present transformation inserts a nitrogen atom between the silyl enol ether olefinic carbons with the concomitant cleavage of the C═C bond. 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*-amido alkylating agents enables modular derivatization with carbon and heteroatom nucleophiles and the unique late-stage editing of carbon frameworks. The reaction efficiency of this transformation is well correlated with enol ether nucleophilicity as described by the Mayr *N* scale. Applications presented herein include late-stage nitrogen insertion into carbon skeletons of 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]

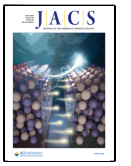
Of particular interest are electrophilic ammonia surrogates, which allow nitrogen incorporation without the requirement for specific substituents. Within this area of investigation, ammonium salts in the presence of an iodine(III) reagent have shown considerable promise[10] since their first report in 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.[11,13]

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 a nitrene-like intermediate. Successful implementation of this strategy would allow manipulation of the 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 has largely been 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).

RESULTS AND DISCUSSION

We began our exploration by subjecting *tert*-butyldimethylsilyl enol ether **1a-TBS** to $PhI(OAc)_2$ (2.5 equiv) and NH_2COONH_4 (1.5 equiv) in MeOH (see Figure 2, entry 1). Gratifyingly, the *N*-acyl-*N*,*O*-acetal product **1b** was obtained in a 59% yield by NMR. This product represents a formal four-electron oxidation of the silyl enol ether, in line with reported "iodonitrene" reactivity.[10] Intrigued by this unusual and valuable C═C cleavage product, we commenced

Received: May 24, 2024
Revised: June 26, 2024
Accepted: June 27, 2024
Published: July 16, 2024



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J. Am. Chem. Soc. 2024, 146, 21129−21136

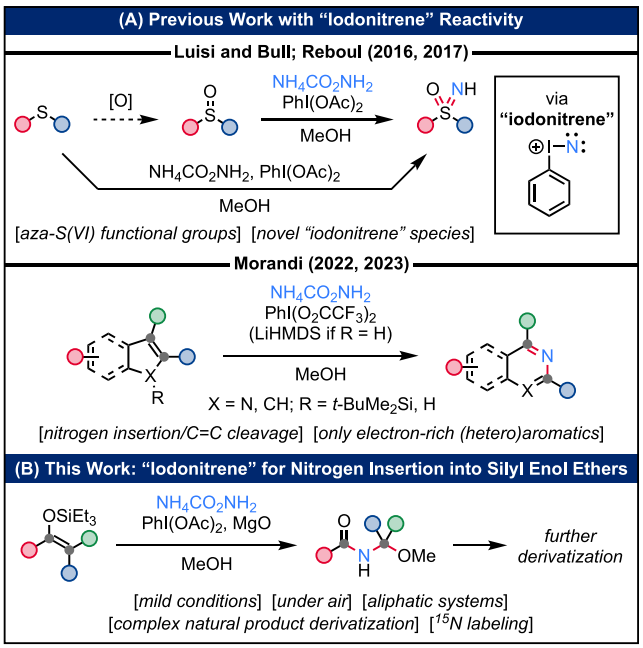
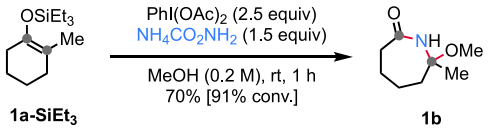


Figure 1. (A) Selected synthetic applications of newly developed "iodonitrene" chemistry. (B) This work: leveraging "iodonitrene" chemistry for oxidative nitrogen insertion into silyl enol ethers derived from aliphatic systems.

Selected Optimization Results



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

entry	variation from conditions above	% NMR yield [% NMR conversion]
1	t-$BuMe_2Si$ instead of $SiEt_3$	59 [90]
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. Selected reaction optimization. *NMR yields refer to the corresponding OEt and O*i*-Pr compounds, respectively.

the optimization of the reaction conditions. Upon screening common silyl groups, we discovered that the triethylsilyl ($SiEt_3$) group gave the highest yield (Figure 2), presumably due to the optimal balance of steric bulk and stability toward the reaction conditions. All subsequent screenings 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 product formation in aprotic solvents (see the Supporting Information). When using 2.5 equiv of $PhI(OAc)_2$, incomplete conversion occurred. Increasing the amount of $PhI(OAc)_2$ to 4.0 equiv ensured complete conversion and maximal yield of **1b** (entry 8). The concentration also plays a fairly significant role, as decreasing the concentration from 0.2 to 0.1 M raised the yield to 85% (entry 9). We hypothesized that acetic acid released during the reaction may lower the reaction efficiency, so we screened various additives. Indeed, including solid MgO increased the yield further to 94% (entry 10).

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 (Figure 3). The oxidative nitrogen insertion was first tested on the model substrate **1a** at a 0.5 mmol scale, giving the expected product **1b** in a 90% isolated yield. The reaction was then rerun at a 15 mmol scale, whereupon the yield had only decreased to 76%, indicating that the reaction is amenable to significant scale-up. The reaction also proceeded smoothly with the triethylsilyl enol ethers of unsubstituted 5-, 6-, 7-, 8-, and 12-membered cycloalkanones, giving the corresponding 6-, 7-, 8-, 9-, and 13-membered cyclic *N*-acyl-*N*,*O*-acetals (**2b**−**6b**) in moderate to good yields. A phenyl substituent at the 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 the 7-membered lactam **8b**. The selective nitrogen insertion into the silyl enol ether C═C bond of **8a** showcases the chemoselectivity favoring nucleophilic olefins. 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**. Insertion into a bis-triethylsilyl enol ether in a bicyclo[2.2.2]octane system **11a** gave a single nitrogen insertion product **11b**, with concomitant hydrolysis of the other silyl enol.

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 initially puzzling, a plausible explanation emerged by considering the innate nucleophilicities of the silyl enol ethers. 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, 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 the 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 oxidative nitrogen insertion was also explored for triethylsilyl enol ethers derived from aldehydes and acyclic ketones (Figure 5). The linear silyl enol ether **12a** gave the expected *N*-formyl-*N*,*O*-acetal product **12b** in a relatively poor 28% yield, whereas the α,α-disubstituted **13a** gave **13b** in a 64% yield. These yields are likely also related to intrinsic substrate nucleophilicity. The corresponding *N*-acyl-*N*,*O*-acetals were also obtained from dialkyl (**14b**) and alkyl aryl

https://doi.org/10.1021/jacs.4c07111
J. Am. Chem. Soc. 2024, 146, 21129−21136

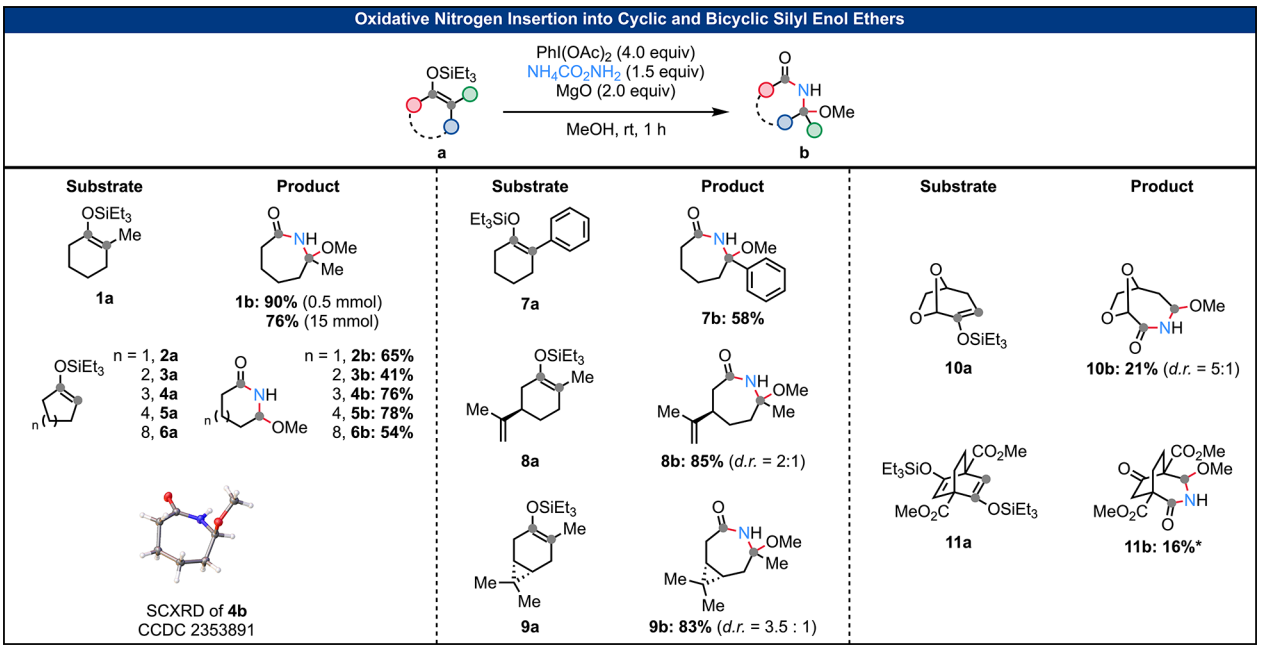


Figure 3. Scope of oxidative nitrogen insertion into cyclic and bicyclic triethylsilyl enol ethers. All reactions were run at 0.5 mmol scale unless indicated. *3.0 equiv of $NH_4CO_2NH_2$, 8.0 equiv of $PhI(OAc)_2$, and 4.0 equiv of MgO.

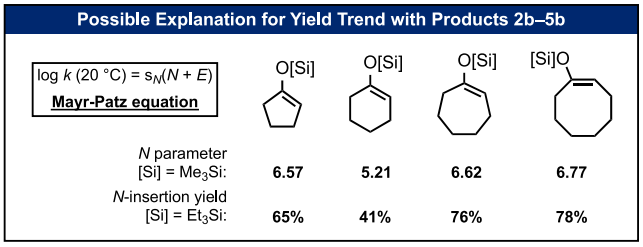


Figure 4. Utilizing Mayr N-parameters to explain the aberrantly low yield of **3b** relative to **2b**, **4b**, and **5b**.

(**15b**) ketones. The range of cycloalkyl phenyl ketones with four- to six-membered cycloalkyl rings was also subjected to the silylation/oxidative nitrogen insertion procedure and provided products **16b**, **17b**, and **24b** in good yields. Intriguingly, the cyclobutyl ring of **16** remained intact with no ring expansion or cleavage products detected. The nitrogen insertion on **16a** was repeated on a 4 mmol scale, giving **16b** in a 74% yield. Next, a range of cycloalkyl (hetero)aryl ketones were explored, allowing us to assess some questions of functional group tolerance. A range of substituted phenyl rings, including CF_3 (**18**), Br (**19**), vinyl (**20**), Cl/F (**21**), OPh (**25**) substituents, as well as a difluorobenzodioxole ring (**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 process. Substrates containing a naphthyl group or a β-phenyl enone also gave the desired *N*-acyl-*N*,*O*-acetals (**22b** and **27b**, respectively). Gratifyingly, quite electron-rich heteroaromatics—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-like conditions.

To investigate the utility of expedient and general access to *N*-acyl-*N*,*O*-acetals, we explored subsequent derivatizations that harness their latent electrophilic nature. The *N*-acyl-*N*,*O*-acetals are air- and moisture-stable sources of *N*-acyl imine or iminium species, which can be generated in situ[18] and intercepted by a nucleophile.[19] Such reactivity allows access to highly congested tertiary amide and lactam nitrogens, which are challenging to access in a modular manner (Figure 7). 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. An analogous combination using trimethylsilyl cyanide as a nucleophile gave the α-amido nitrile **38**. Allylation could also be achieved 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 reaction with a silyl ketene acetal was also successful, giving a very sterically hindered array of vicinal quaternary centers of **40** in a 48% yield. Under Brønsted acid conditions, α-amido sulfide **41** was formed from thiophenol. An Arbuzov-type transformation using trimethylphosphite was

https://doi.org/10.1021/jacs.4c07111
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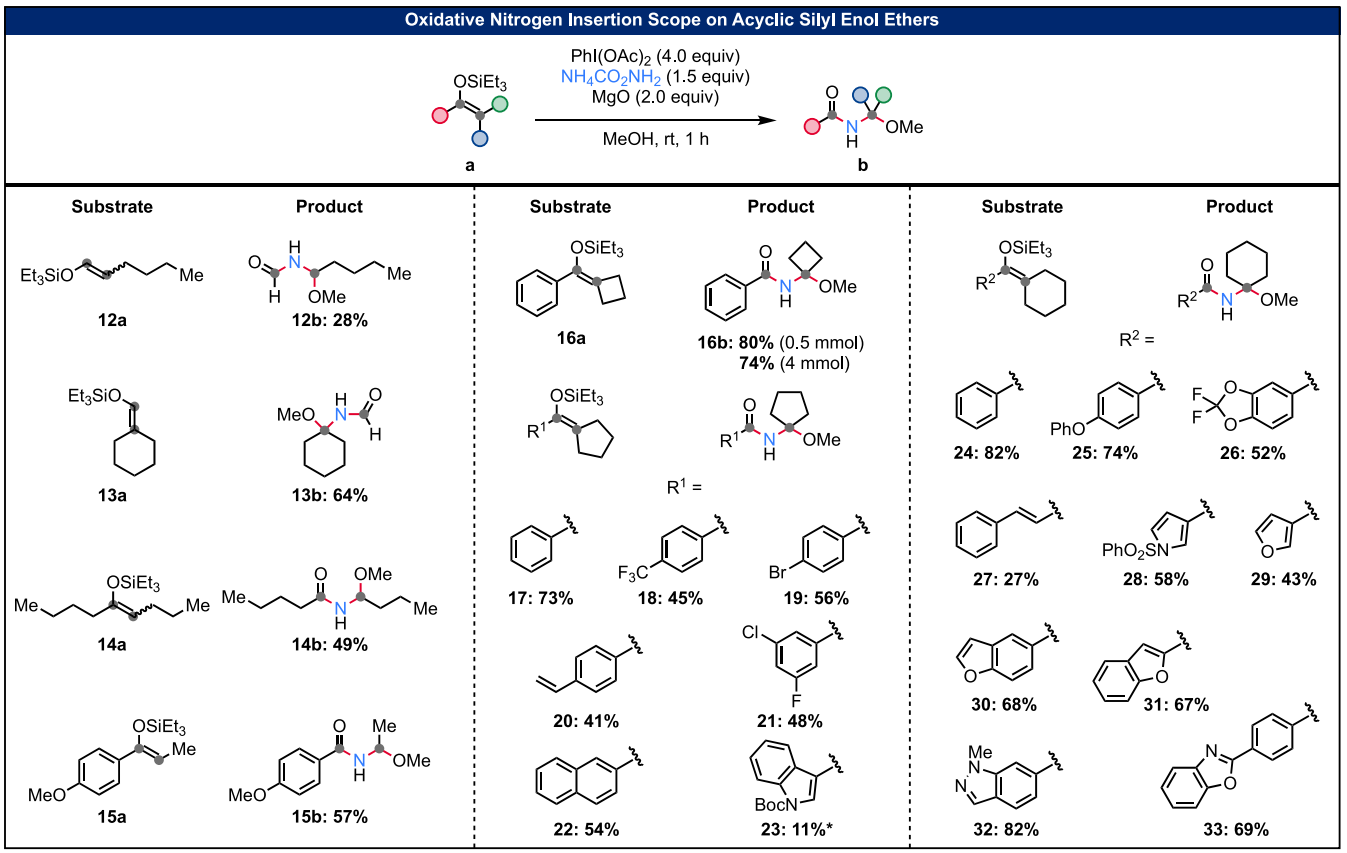

Figure 5. Scope of the oxidative nitrogen insertion into acyclic triethylsilyl enol ethers. All reactions were run at a 0.5 mmol scale unless indicated. *2.0 equiv of $PhI(OAc)_2$.

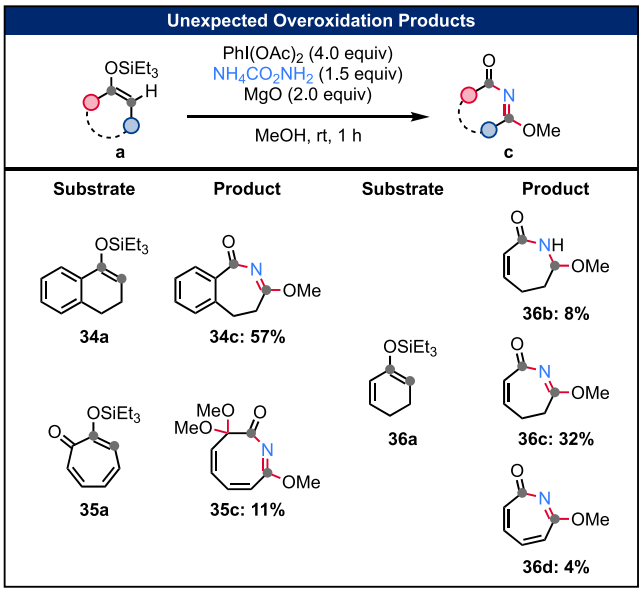

Figure 6. Unexpected overoxidation under standard oxidative nitrogen insertion conditions giving primarily *N*-acyl imino ethers **34c**–**36c** as six-electron oxidation products.

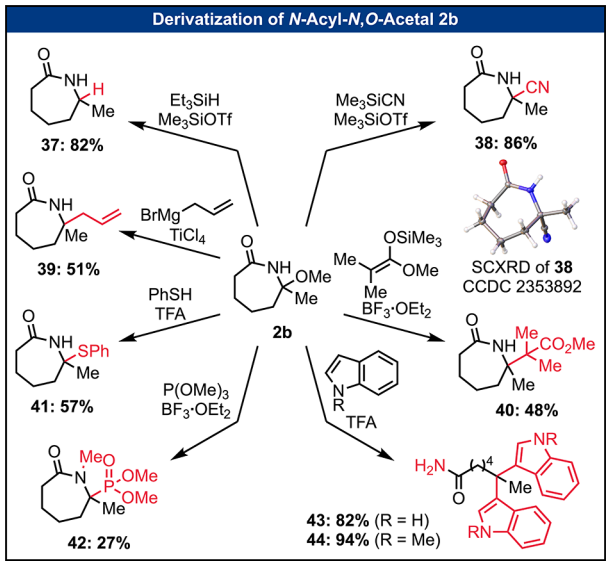

Figure 7. Derivatization of *N*-acyl-*N*,*O*-acetal **2b** showcases the potential for rapid complexity generation.

also successful, giving *N*-methyl-*α*-amido phosphonate **42** in a 27% yield. Lastly, electrophilic aromatic substitution was attempted with NH- or *N*-methylindole. Surprisingly, only the ring-opened, double electrophilic aromatic substitution products **43** and **44** were isolated, even without an excess indole nucleophile. 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.

We also considered oxidative nitrogen insertion as a tool to manipulate carbon skeletons of complex natural products (Figure 8). The commercially available steroid estrone (**45**) was first doubly silylated with Et_3SiOTf and then was subjected to standard nitrogen insertion conditions.

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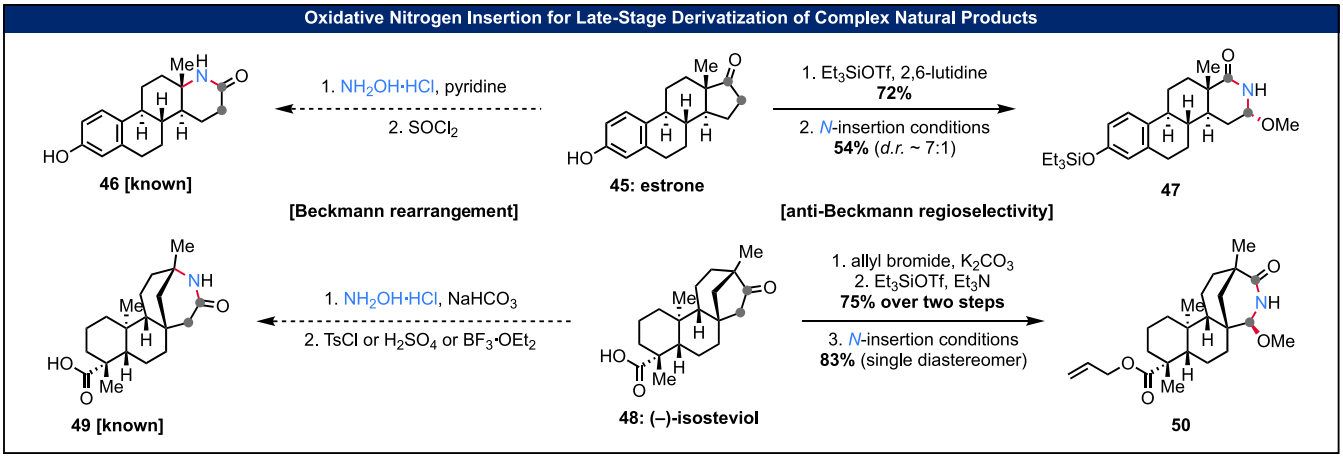

Figure 8. Application of oxidative nitrogen insertion into estrone- and (−)-isosteviol-derived silyl enol ethers **45** and **48**, respectively, with anti-Beckmann regioselectivity. The *N*,*O*-acetals **47** and **50** are primed for further synthetic elaboration.

The expected *N*-acyl-*N*,*O*-acetal **47** was isolated in a 54% yield with a 7:1 d.r. The terpenoid (−)-isosteviol, prepared on a multigram scale from the sweetener stevioside following a reported procedure,[20] was analogously esterified, silylated, and subjected to the standard conditions. The *N*-acyl-*N*,*O*-acetal **50** was isolated in an 83% yield as a single diastereomer. As indicated in Figure 8, both estrone and (−)-isosteviol have previously been transformed into the corresponding ring-expanded lactams **46**[21−23] and **49**[24] using the Beckmann rearrangement,[25] though only the alternative nitrogen insertion into the more substituted side was observed. In general, the regioselectivity of Beckmann rearrangements is stereospecific and depends on the *E*/*Z* preference of the starting oxime, which is not generally controllable.[26−28] Furthermore, fragmentation pathways can occur when one of the oxime substituents strongly stabilizes carbocationic character, such as tertiary alkyl groups or substituents with α-heteroatoms.[29] Indeed, such fragmentation was observed during the preparation of **49**.[24] Other commonly used methods for the conversion of ketones to amides/lactams include the Schmidt−Aubé reaction,[30,31] where the latent electrophilic nitrogen source is either hydrazoic acid[32] or an alkyl azide.[33] While rules have been formulated regarding the regiochemical outcome of the Schmidt-Aubé reaction, the site of nitrogen insertion is still predominantly dictated by migratory ability and substrate structure.[28,33,34] In contrast, the present method is not bound by considerations of oxime geometry or migratory aptitude as the site of nitrogen insertion is precisely dictated by the regiochemistry of the silyl enol ether. Furthermore, the *N*,*O*-acetal afforded here can be a new vector for further synthetic elaboration. Such an 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 nitrogen insertion presented here for ^{15}N isotopic labeling of amides and lactams. Selective labeling with ^{15}N is important for a variety of tools to interrogate biomolecule structure[35−37] and function,[38−40] including MS-based proteomics[41] and metabolomics,[42−44] spin hyperpolarization,[45−47] and mechanistic elucidation.[48,49]

Since $^{15}NH_4Cl$ is one of the most common and relatively inexpensive commercially available ^{15}N sources, it was preferable to establish conditions for nitrogen insertion directly with commercial $^{15}NH_4Cl$. NH_4Cl performed quite poorly during the initial screening of nitrogen sources (see the Supporting Information). We wondered if it was possible to generate ^{15}N-labeled isotopologues of more efficient ammonium salts in situ via salt metathesis. After a short optimization campaign, we gratifyingly found that the combination of NH_4Cl and Ag_2CO_3 was suitable for generating the desired *N*,*O*-acetal **1b** (Figure 9 and Supporting Information),

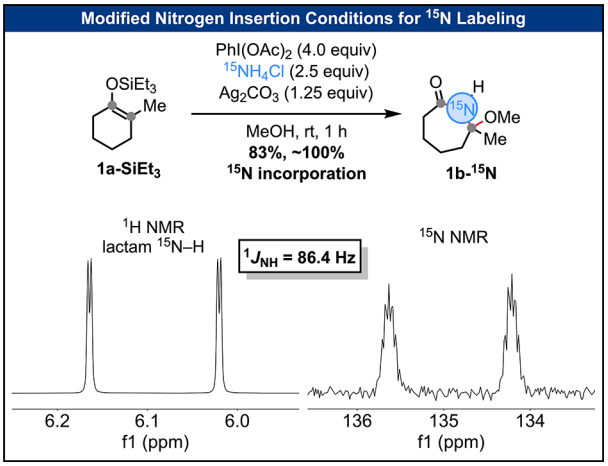

Figure 9. In situ generation of $(^{15}NH_4)_2CO_3$ for ^{15}N insertion into **1a-SiEt$_3$**. ^1H and ^{15}N NMR showing the large $^1J_{NH}$ coupling constant in **1b-^{15}N**.

presumably via $(NH_4)_2CO_3$ upon the precipitation of AgCl. Use of these modified conditions with $^{15}NH_4Cl$ afforded **1b-^{15}N** in an 83% yield with essentially 100% ^{15}N incorporation, as shown by the absence of a ^{14}NH peak in the ^1H NMR spectrum (see Figure 9, bottom-left spectrum).

A plausible mechanistic pathway for this transformation is outlined in Figure 10. Formation of the C=C cleavage product *N*-acyl-*N*,*O*-acetal **D** can be rationalized on the basis of C−C cleavage from an *N*-iodo aziridine species such as **B** (Figure 10) or a similar aziridine with an *N*-leaving group. Such a mechanistic step would initially afford *N*-acyl imine **C**, which would then afford the observed product **D** upon addition of methanol solvent. Formation of the key aziridine **B** can be envisioned as a formal [2 + 1] cycloaddition involving a suitable nitrene equivalent after four-electron oxidation by 2

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J. Am. Chem. Soc. 2024, 146, 21129−21136

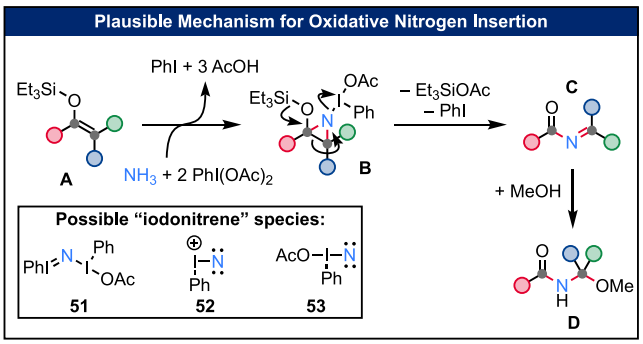

Figure 10. Plausible mechanism for oxidative nitrogen insertion into silyl enol ethers with speculative structures for the "iodonitrene" intermediate.

equiv of $PhI(OAc)_2$. Although the exact nature of the aziridination reagent is not clear, potential candidates may include *N*-iodo-iminoiodinane **51**, as well as related free nitrenes **52** and **53**, previously proposed on the basis of MS experiments.[6,11] The lack of two-electron oxidation products in favor of available four-electron pathways suggests that 1 equiv of ammonia must react with 2 equiv of the iodine(III) reagent to form the active aminating species,[12] as opposed to stepwise aziridination with iminoiodinane (PhI=NH) and subsequent oxidation/rearrangement of the intermediate N–H aziridine.

CONCLUSIONS

We have developed a robust method to perform oxidative insertion of nitrogen into the C=C bond of silyl enol ethers. The present method exemplifies a new mechanistic paradigm for 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 under air and shows good tolerance of a wide variety of substituents and functional groups. 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 also showed 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 at https://pubs.acs.org/doi/10.1021/jacs.4c07111.

Detailed experimental procedures and analytical data (PDF)

Accession Codes

CCDC 2353891–2353892 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

†A.G. and S.Y. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Pierre Loch-Temzelides for providing compound **11a**. We also thank Prof. Raúl Hernandez Sanchez and Mohammed Bilal for assistance with SCXRD data, Augustin Rodriguez for assistance with HRMS data, and Andrew Maughon for synthetic assistance. Z.B. gratefully acknowledges support from the Robert A. Welch Foundation (C-1680) and the National Science Foundation (CHE-2203948). L.K. gratefully acknowledges support from the National Institutes of Health (R35 GM-136373) and the Robert A. Welch Foundation (C-1764).

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https://doi.org/10.1021/jacs.4c07111
J. Am. Chem. Soc. 2024, 146, 21129−21136