A Synthetic Cycle for Heteroarene Synthesis by Nitride Insertion

Patrick Q. Kelly, Alexander S. Filatov, Mark D. Levin*

Department of Chemistry, University of Chicago, Chicago, Illinois 60637, United States

Abstract: [cis-terpyOsNCl2]PF6 inserts nitrogen into indenes to afford isoquinolines. The insertion proceeds through an azaallenium intermediate, with mechanistic and computational studies suggesting that azaallenium formation occurs via a stepwise aziridination followed by electrocyclic ring opening. Examination of a substrate diverted from aromatization resulted in inner-sphere ligand rearrangement to afford an azaallyl chloride complex; kinetic studies suggest this species forms via an analogous azaallenium intermediate. Studies on base-promoted release of the isoquinoline suggest that the azaallyl chloride is not an obligate intermediate for aromatization and the parent azaallenium can directly eliminate to give a neutral dichloroosmium(II)-isoquinoline intermediate. The heteroarene can subsequently be thermally liberated to afford an osmium(II) acetonitrile complex, which can be oxidized to regenerate the nitride over two steps. First, in the presence of ammonia, oxidation affords an osmium(III) amidine, with subsequent oxidation in the presence of toluene sulfonic acid ultimately regenerating the nitride. The mechanistic foundation set by this synthetic cycle opens the door to the further development of nitrogen insertion heteroarene syntheses promoted by late transition metal nitrides.

Main Text: Homogeneous transition-metal-catalyzed nitrene transfer to organic substrates is a remarkably useful strategy to synthesize high value nitrogen-containing compounds including aziridines, pyrroles, and amines.1–11 Typically, these reactions occur via the intermediacy of terminal metal imido or metallonitrenoid species.12–17 By contrast, nitrogen transfer from terminal metal nitrido complexes is much less explored despite their unique and often attractive reactivity.12,14,18–21 Indeed, only recently has the first example of catalytic nitrogen atom transfer to organic substrates from a well-characterized terminal metal nitride been reported.22 Instead, the majority of studies on terminal metal nitrides focus on N2 reduction and valorization by early transition metals.23–30 These early metal nitrides are typically nucleophilic at N due to polarization of the HOMO away from the relatively high energy metal d-orbitals.31 By the same analysis, group 8 metal nitrides often behave as electrophiles at nitrogen32 and have shown distinct stoichiometric reactivity with potential for remarkable utility in synthetic organic chemistry.

Meyer’s seminal work on cationic osmium(VI) nitrides ignited interest in this area by demonstrating their reactivity with a variety of nucleophiles (eg. PPh3, N3-, RSH, etc.).33 Subsequently, Mayer extended this reactivity to organic nucleophiles, including nitrogen insertion to B-C bonds.34–36 Additionally, Lau has demonstrated the propensity for cationic ruthenium(VI) nitrides to perform aziridinations and C-H activations in the presence of pyridine.37,38 The same group has more recently reported photochemical
C–H activation by an anionic osmium(VI) nitride. The present report was inspired in particular by reports from the Brown group, demonstrating that cationic, terminal osmium(VI) nitrido complexes can insert nitrogen into conjugated olefins (Figure 1A).

With this precedent in mind, we envisioned analogous N-atom insertion to cyclic olefins as an attractive route to heterocycles upon aromatization of the intermediate azaallenium species. We report here the successful realization of a 5-step synthetic cycle which enables the formal insertion of a nitrogen atom into an indene and regeneration of the parent osmium nitride (Figure 1B). Below, the development of this cycle and mechanistic aspects elucidated along each step are discussed.

While previous reports have demonstrated that 6- and 7-membered cyclic olefins can undergo N-atom insertion, Brown reported that the reaction of 1 with cyclopentadiene did not afford any discernible products. In spite of these reports, our initial studies exploring the reactivity of [cis-terpyOsNCl2]PF6 (1) showed that indenes were productive substrates provided that an additional element of conjugation was present. (The parent indene behaved similarly to cyclopentadiene.) As such, 3-phenyl-1H-indene (2a) was chosen as a model substrate. Heating 1 at 50 °C in the presence of excess 2a, we observed a modest yield (27%) of the expected insertion product 1-phenylisoquinoline. When the reaction was instead conducted at ambient temperature, the azaallenium 3a could be isolated by precipitation with Et2O in 77% yield (Figure 2A). 1H NMR analysis indicates a doublet of doublets at δ 6.61 ppm, which corresponds to the OsCH, split by the diastereotopic set of methylene protons. HSQC indicates this proton is coupled to an sp3 carbon with δ 44.4 ppm, which we assign to OsCH in agreement with precedent. Attempts to crystallize this structure from MeCN solutions resulted in spontaneous aromatization of the azaallenium ligand with loss of HCl to afford [(terpy)OsCl(NCMe)(1-phenylisoquinoline)]PF6 (7). In weakly-coordinating solvents, crystals suitable for X-ray diffraction could only be grown upon exposure to air, affording the analogous aromatized Os(III) isoquinoline complex (see SI).

With the goal of disfavoring aromatization to obtain crystallographic evidence for the azaallenium, we replaced 2a with 1,1-dimethyl-3-phenylindene (2f, Figure 2B). Surprisingly, rather than affording an analogous azaallenium, 1 reacts cleanly with 2f to afford a crystallographically characterized aza-allyl chloride (8). HSQC confirms that the singlet in the 1H NMR spectrum assigned to CCl is coupled to a strongly deshielded sp3 carbon at δ 90 ppm, which diverges substantially from both 3a and from previously reported azaallenium complexes, instead aligning more closely with previously reported N-chloroalkylpyridinium salts. Density functional theory (DFT) modeling of the azaallenium energies at the B3LYP-D3/6-311g(d,p)(C,H,N,Cl)/SDD(Os)-PCM(MeCN)//B3LYP-D3/6-31g(d,p)(C,H,N,Cl)/SDD(Os)-PCM(MeCN) level of theory show a stark decrease in stability of the azaallenium isomer relative to the aza-allyl chloride upon introduction of the methyl groups, presumably due to steric clashes between the methyl groups and the equatorial ligands (see SI for details).

These observations raise a mechanistic question regarding the primacy of either the azaallenium or azaallyl chloride on the reaction coordinate. Based on the observed displacement of chloride upon attempted crystallization of 3a, we hypothesized that the aza-allyl chloride 8 results from solvolysis of 3f. Indeed, monitoring the reaction of 1 with 2f by NMR indicates the buildup of an intermediate which we tentatively assign as the dimethylated azaallenium 3f. This species quickly decomposes to give 8 prior to full consumption of the starting material. 3f builds to a maximum total concentration at approximately 80% conversion of 1, at which point 3f and 8 were observed in 69% and 13% yield respectively (representing 88% of total mass balance), and the kinetic behavior was well-approximated by a pseudo-first order A → B → C model with roughly 5-fold faster consumption of 1 than of 3f. By contrast, reaction of 1 with 2a directly affords the azaallenium 3a in 95% yield by NMR with no observable intermediates. Both reactions exhibit first order kinetics in 1 under pseudo-zero order concentrations of 2. The reaction with 2a is unsurprisingly faster (k ≈ 0.14 M−1 s−1) than with 2f (k2 ≈ 0.05 M−1 s−1) likely due to increased steric around the olefin.
Figure 2: a) Reaction of 2a with 1, NMR evidence for azaallenium 3a, crystallographic characterization of aromatized product, and Hammett study of reaction rate (separate-pot, pseudo-first-order \( k_{\text{obs}} \), \( n = 3 \)).
b) Reaction of 2f with 1, crystallographically characterized azaallyl chloride 9, and kinetic data at 25 °C indicating formation of intermediate 3f, fit to an A → B → C model.

To better elucidate the mechanism for the formation of 3, we conducted a Hammett analysis by varying the substituent on the aryl group (Figure 2A). The strong correlation between reaction rate and \( \sigma^+ \) (\( \rho = 1.4, R^2 = 0.996 \)) supports significant carbocation character developing at the doubly benzylic position.\(^{44,45}\) We interpret the relatively small \( \rho \) as indicative of an early transition state for attack rather than as evidence for radical character on the basis of the far poorer correlation with Creary’s \( \sigma^\bullet \) scale (\( R^2 = 0.698 \)).\(^{46}\)

Modeling of the reaction sequence from 1 to 3a by Density functional theory (DFT) agrees with this experimental assessment and predicts an aziridination-electrocyclic ring opening sequence (Figure 3). Direct nucleophilic attack of the olefin at the nitride ligand proceeds with a modest energy barrier (TS1) to a carbocation-like intermediate (INT1), in agreement with our Hammett analysis. Ring-closing completes the stepwise aziridination to give INT2.\(^{38}\) C-C bond cleavage can proceed through TS3 (reminiscent of haloaziridine electrocyclic ring opening)\(^{47,48}\) to give the unobserved azaallenium isomer 3a*. This species can isomerize to the observed, more stable isomer 3a through an “allene-rock” mechanism.\(^{41}\) Our calculations additionally suggest that the reaction of the analogous ruthenium(VI) nitride is also feasible through the same pathway (See SI for details). However, the ruthenium analog of 1 has not been reported and our preliminary attempts towards its preparation were unsuccessful.
Release of the isoquinoline from osmium can be induced by heating 3a with triethylamine (Et\textsubscript{3}N) in MeCN, affording 1-phenylisoquinoline (4) and the neutral osmium(II) acetonitrile complex 5, each in 60% yield, along with a 35% yield of 7 (the cationic product observed upon crystallization of 3a, Figure 4A). The structure of 5 was confirmed by independent synthesis from the reaction of [\textit{trans-}terpyOsNCl\textsubscript{2}]PF\textsubscript{6} with NBu\textsubscript{4}N\textsubscript{3}.\textsuperscript{49} Treatment of 3a with trialkylamine at room temperature instead results in the rapid formation of (terpy)Os(1-phenylisoquinoline)Cl\textsubscript{2} (9), which was isolated in 79% yield and characterized crystallographically. (Tributylamine was employed preparatively to aid in separation of the ammonium salt.) These observations, coupled with the above kinetic data, in turn raise the question of whether an azaallyl chloride analogous to 8 is an intermediate for the formation of 5, 7, and/or 9.

Addition of 2 equivalents of exogenous tetrabutylammonium chloride (NBu\textsubscript{4}Cl) to the base-mediated thermolysis of 3a did not significantly alter the ratio of 5 and 7. Additionally, no 9 is observed upon refluxing 7 with NBu\textsubscript{4}Cl. Together, these observations suggest that chloride dissociation is irreversible. Given the maintenance of both chloride ligands in 9, an azaallyl chloride intermediate can only be accommodated in its formation if either (i) it forms without association of an acetonitrile ligand, or (ii) internal return of the chloride from the azaallyl fragment is more effective at displacement of acetonitrile than exogenous chloride.

Heating 9 in MeCN results in a 76% yield of isoquinoline 4 along with an 16% yield of 7 and an 80% yield of 5. Addition of Et\textsubscript{3}N and NH\textsubscript{4}PF\textsubscript{6} (to mimic the conditions in the thermolysis of 3a) does not affect this observed ratio of products. Because this distribution diverges meaningfully from the product ratio observed in the reaction of 3a, it is likely that 3a does not evolve exclusively through the formation of 9 when heated in the presence of triethylamine. While we cannot therefore rule out the azaallyl chloride as relevant, the balance of evidence suggests it is not an obligate intermediate in the aromatization process.
Figure 4: a) Release of isoquinoline facilitated by base, evidence for direct deprotonation of 3. b) Oxidation and regeneration of the nitride through stepwise cleavage of coordinated acetonitrile. *NMR yield vs. internal standard.

Completion of a full synthetic cycle from the osmium(II) dichloride 5 requires four-electron oxidative N-atom transfer to the metal center. Only one well-characterized example of such an oxidative N-atom transfer has been reported. Alternatively, oxidation of a coordinated ligand may regenerate the nitride; Meyer has reported electrochemical oxidation of osmium-ammine complexes. Inspired by this precedent, we examined the reaction of 5 with a variety of oxidants and ammonia sources. Surprisingly, the use of PhI(OAc)\(_2\) and ammonium carbamate or ammonium acetate afforded instead the osmium(III) acetamidine product (6, Figure 4B). Oxidation of 5 with an excess of PhI(OAc)\(_2\) in the absence of ammonium sources results in the predominant formation of dichloro(terpy)osmium(III) monoacetonitrile. While unexpected, the observation of 6 inspired us to consider nitride generation via C≡N bond cleavage of the acetonitrile ligand. Accordingly, oxidation of 6 in the presence of p-toluenesulfonic acid gives a 4:3 mixture of cis- and trans-nitrides, isolated as chloride salts. This initially gives the trans-osmium(VI) nitride, which is observed in 75% NMR yield after 5 minutes. Trans-cis isomerization of the osmium(VI) nitride is well precedented, and can be driven to completion by heating in MeOH with an excess of lithium chloride, regenerating 1 to complete the synthetic cycle.

In conclusion, we have demonstrated a synthetic cycle for the synthesis of isoquinolines from indenes via direct N-atom insertion from an osmium(VI) nitride, which sets the stage for the ultimate development of catalytic processes that follow this template. We have additionally shown that azaallenium formation occurs via a stepwise aziridination/ring-opening sequence. Aromatization of this species is dominated by direct base-assisted deprotonation, though solvent-assisted migration of the chloride ligand cannot be ruled out as an additional pathway. Finally, we have demonstrated the stepwise oxidative cleavage of an acetonitrile ligand to regenerate the nitride. The nitrogen insertion is computationally feasible for both osmium(VI) and ruthenium(VI) nitrides, suggesting that both metals hold potential for heteroarene synthesis by nitrogen insertion. The mechanistic studies herein shed light on metal nitride insertion processes and point the way towards catalysis via regeneration of the nitrido-ligand.
Supporting Information

Experimental procedures and characterization data (PDF)

Accession Codes

CCDC 2174517 – 2174521, 2184500 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.

AUTHOR INFORMATION

Corresponding Author
* Mark D. Levin (marklevin@uchicago.edu)

ACKNOWLEDGMENT

Prof. John Anderson and Dr. Tyler Pearson are thanked for helpful discussions. The Packard Foundation and National Institutes of Health (R35 GM142768) are thanked for funding. The crystal structure of 7 was collected at ChemMatCARS Sector 15 which is supported by the NSF under grant number NSF/CHE-1834750. This research used resources of the APS, a U.S. DOE Office of Science User Facility operated for the DOE Office of Science by Argonne National Laboratory under Contract No. DE-AC02-06CH11357. We would like to thank Dr. Yu-Sheng Chen for assistance with SXRD acquisition at 15-ID-B,C,D. Dr. Andrew McNeese, Dr. Kate Jesse, and Sophie Whitmeyer are thanked for help with SXRD. Dr. Josh Kurutz is thanked for help with NMR experiments. We acknowledge the University of Chicago Research Computing Center (RCC) for computational resources.

REFERENCES


