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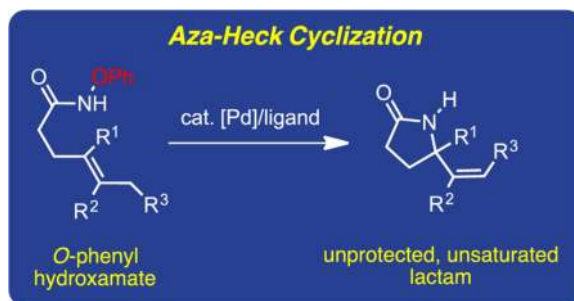
Synthesis of Secondary Unsaturated Lactams via an Aza-Heck Reaction

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Abstract

The preparation of unsaturated secondary lactams via the palladium-catalyzed cyclization of *O*-phenyl hydroxamates onto a pendent alkene is reported. This method provides rapid access to a broad range of lactams that are widely useful building blocks in alkaloid synthesis. Mechanistic studies support an aza-Heck-type pathway.

Graphical Abstract



Small nitrogen-containing heterocycles, such as pyrrolidines, pyrrolidinones, piperidines, and piperidones, are ubiquitous in both synthetic and naturally occurring bioactive compounds.¹ Secondary, N-H bearing, allylic lactams are highly valued synthons for accessing a diverse array of such ring systems embedded within complex structures. In addition, allylic lactams themselves are prevalent scaffolds within bioactive molecules.²

An attractive approach to these compounds involves cyclization of a primary amide (or equivalent) onto a pendant alkene using transition metal catalysis. The aza-Wacker reaction presents one approach to such a transformation; however, these reactions are not well developed for amides as they typically require highly acidic nitrogen nucleophiles, such as sulfonimides.³ While a few cyclizations of secondary amides (or related compounds) leading to tertiary amides are known,⁴ only a single example of an aza-Wacker cyclization of a

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ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge on the ACS Publications website.

primary amide leading to an unprotected secondary lactam has been reported,⁵ drawing into question the generality of this approach (Figure 1, top).

In contrast to the use of nucleophilic nitrogen in aza-Wacker reactions, we envisioned that an umpolung strategy involving electrophilic nitrogen could provide an alternative lactam synthesis via an aza-Heck cyclization. Reactions involving nitrogen electrophiles are a burgeoning area of chemical research,^{6,7,8,9,10,11,12} however, aza-Heck reactions remain nascent.¹³ In pioneering studies, Narasaka,¹⁴ Bower,¹⁵ and others¹⁶ have demonstrated that *O*-acyl ketooximes can participate in various types of aza-Heck cyclizations. This work has established this method as a powerful entry into cyclic ketimines and related aromatic aza-heterocycles (Figure 1, middle). Very recently, Bower reported the cyclization of unsaturated *N*-acyloxysulfonamides.¹⁷ However, other classes of electrophilic nitrogen centers have not been reported in aza-Heck reactions.¹⁸ In particular, no examples of aza-Heck reactions of *N*-H bearing nitrogen electrophiles have been described.

In the context of our group's standing interest in heteroatomic-Heck reactions,¹⁹ we sought to identify an appropriate nitrogen electrophile to allow direct lactam synthesis (Figure 1, bottom). Herein, we disclose an aza-Heck reaction using *O*-phenyl hydroxamates that provides access to a variety of unprotected allylic lactams. Utilizing a commercially available catalyst system, this reaction allows the direct synthesis of unprotected allylic lactams with broad substrate scope and exceptional functional group tolerance.

Inspired by Liebeskind's copper-catalyzed arylation studies,^{6c,20} we first investigated the cyclization of *O*-benzoyl hydroxamate ester **1** under conditions reminiscent of our other heteroatomic-Heck reactions (5 mol% (COD)Pd(CH₂SiMe₃)₂, 7.5 mol% P^tBu₃, Et₃N, DMF, 80 °C). Under these and similar conditions, none of the desired product was observed (Table 1, entry 1). Instead, several undesired products (most notably the symmetric urea **5**, attributable to Lossen rearrangement,²¹ along with lesser amounts of primary amide **6** were formed. Similar results were obtained with a more electron-deficient ester (entry 2). Numerous other highly activated hydroxamate ester derivatives (not shown) proved to be unstable during preparation.

Based upon these results, we decided to investigate less activated hydroxamate derivatives. Following this reasoning, we were highly encouraged to find trace yield of the desired [6,5]-fused lactam **4** when the cyclization of *O*-phenyl hydroxamate ether **3** was investigated under these conditions (Table 1, entry 3). Also significant, no Lossen byproducts were observed. With a promising electrophile in hand, the role of ligand was investigated. Using triphenylphosphine (entry 4) both improved the yield of **4** and lowered the relative production of **5**. This trend was even more pronounced with use of tris(3,5-bis(trifluoromethyl)phenyl)phosphine, an electron-deficient ligand that has been successfully used by Bower (entry 5).

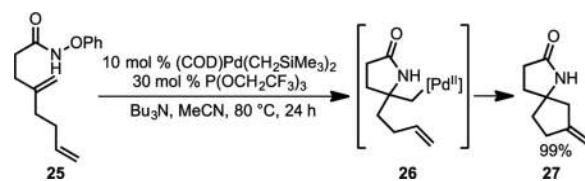
We postulated that the relative success of these aromatic ligands might lie in part to their π -acidity, which might serve to stabilize the putative palladium intermediates that bear multiple π -donor ligands. This line of reasoning led us to investigate other electron-deficient ligands. Triethylphosphite was notable in this regard, providing the product in a similar yield

(12%) but with much less primary amide side-product (entry 6). Further optimization using triethylphosphite revealed that increasing the ligand-to-metal ratio to 3:1, changing the solvent to acetonitrile, decreasing the reaction concentration, switching the base to Bu₃N, and slightly increasing the catalyst loading provided improved yields of **4** (entry 7).²² While these improvements provided reasonable production of the desired product, reduced side product was still observed. Further investigation revealed that the use of commercially available tris(2,2,2-trifluoroethyl)phosphite was able to largely avoid the formation of the reduced side product.²³ With this ligand, **4** was isolated in near quantitative yield (entry 8).

The scope of the reaction was next explored (Scheme 1). Like **4**, [5,5]-fused lactam **7** was prepared in high yield. As expected, both **4** and **7** were formed as a single *syn* diastereomer. Product **8** demonstrated that acyclic substrates are also viable, and *exo*-cyclic alkenes can be prepared with high levels of stereocontrol. Isoindolinone **9** was formed in high yield as a single alkene isomer. In this case, we believe enamide formation is thermodynamic in nature, and is the result of isomerization of the initially formed terminal alkene.²² Substitution adjacent to the carbonyl was tolerated using the fluorinated ligand. For example, **10** was isolated in 76% yield. Similarly, mono-methyl **11**, as well as the α -*N*-Bocamine **12**, were readily prepared, albeit without significant diastereoselectivity. In contrast, substitution at the β -position significantly influences the stereochemical outcome of the reaction (**13**).²⁴ Trisubstituted alkenes are competent substrates for this aza-Heck reaction, and can be used to prepare both spirocyclic (**14**) and other lactams (**15**) bearing fully substituted carbon centers. Remarkably, even tetrasubstituted alkenes can be cyclized. For example, the highly substituted isoindolinone **16** was isolated in 96% yield. This is the first example of a tetrasubstituted alkene participating in an aza-Heck reaction.

With only a few exceptions,^{16d, 25} all prior examples of aza-Heck reactions have been limited to the formation of simple or fused 5-membered rings. It is thus particularly notable that the bridged bicycle **17** can be readily prepared using this chemistry. This is one of the first examples of a transannular cyclization within this class of reactions.¹⁷ In addition, although attempted formation of **18** resulted in only reduction of the starting material, formation of the δ -lactam bearing a fused aromatic ring (**19**) proceeded smoothly. This latter cyclization provides the prospect that further studies will be able to expand the scope of these cyclizations to larger ring systems.

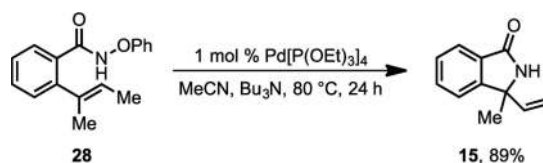
This method is broadly tolerant of functional groups, as revealed by a stoichiometric additive study.^{22, 26} Tolerated additives include carboxylic acids, nitroalkanes, phenols, benzaldehydes, styrenes, nitrobenzenes, thiophenes, indoles, imidazoles, pyrazoles, primary anilines, and benzonitriles. In addition to these additive studies, several functionalized products were also prepared. For example, benzodioxazole **20** and the pyridyl-based **21** were both isolated in high yield (Scheme 1). Thiophene **22** was not observed; however (based upon the additive screen) we believe this is a function of ring strain of the product, and not due to interference of the heterocycle.²² Activation of the hydroxamate occurs in preference to both aryl chlorides and aryl bromides (**23** and **24**), providing opportunities for additional functionalization.



(1)

To further explore the utility of this transformation in the preparation of complex ring systems, we explored the possibility of a tandem aza-Heck/Heck sequence. Much to our delight, subjecting diene **25** to the reaction conditions provided a near quantitative yield of spirocycle **27** (eq 1). This result is consistent with a tandem cyclization proceeding via the neopentyl palladium complex **26**.^{27,28}

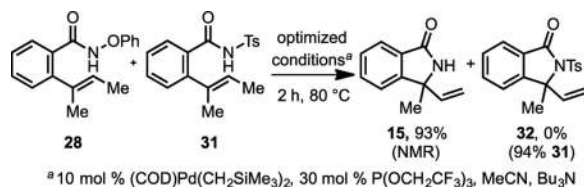
In principle, this reaction could proceed either via an aza-Wacker or an aza-Heck mechanism. The former would involve Pd(II) activation of either the N–H bond or the alkene; the latter would involve Pd(0) activation of the N–O bond. Circumstantial evidence suggests that the mechanism does not involve a Wacker mechanism, as aza-Wacker reactions of aromatic hydroxamate esters are known (for both *O*-Me and *O*-Bn) substrates, and they lead to cyclic hydroxamates retaining the N–O bond.^{4b, 4e}



(2)

To further probe the mechanism, several studies were undertaken. First, although other Pd(0) complexes such as Pd₂dba₃ provide ineffective catalysis (likely due to competitive ligation of the dba),²² Pd[P(OEt)₃]₄ is an extremely competent catalyst (eq 2). With only 1 mol % of this complex, high yield of **15** is observed.²⁹ This result demonstrates that a Pd(II) precatalyst is not required.

Second, independent cyclization of each isomer of alkene **29** reveals the reaction is stereospecific (Scheme 2). Cyclization of (*Z*)-**29** leads exclusively to enamide (*Z*)-**30** (*E/Z* >1:99), independent of reaction time. In contrast, subjecting (*E*)-**29** leads predominately to (*E*)-**30** (*E/Z* = 91:9) after 15 minutes. After longer reaction times, however, this ratio erodes to *E/Z* = 60:40, indicating that (*E*)-**30** is kinetically formed and slowly converts to the more stable *Z*-isomer. The kinetic selectivity is consistent with a pathway defined by suprafacial migratory insertion of a Pd–N bond, C–C σ -bond rotation, and *syn* β -hydride elimination. This outcome rules out a mechanism initiated by Pd(II) activation of the alkene followed by antarafacial attack of nitrogen, but is consistent with either a Heck-like pathway involving N–O activation or a Wacker-like pathway involving initial N–H activation.^{30,31}



(3)

Finally, we have examined the viability of *N*-acyl sulfonamides as substrates. These highly acidic compounds (pKa ~2) are known to participate in aza-Wacker reactions via N–H activation.^{4d} Either alone,²² or in the presence of an *O*-phenyl hydroxamate **28** (eq 3), *N*-acyl sulfonamide **31** does not undergo cyclization under our conditions. This result argues against a Wacker-like mechanism involving N–H activation and precludes the possibility that the hydroxamates are serving simply as a terminal oxidant. Similar studies also show that primary amides are not substrates for the reaction.^{22,32}

Based upon the above evidence, we currently favor a Heck-like pathway involving oxidative addition into the N–O bond, followed by suprafacial migratory insertion and syn β-hydride elimination (Figure 2). To date we have not been able to directly observe adducts from metal insertion into the N–O bond, however, further studies are ongoing to elucidate the details of that step of the mechanism.^{33,34,35}

In summary, we have developed a mild, catalytic method for the synthesis of unsaturated secondary lactams. This reaction boasts a broad substrate scope, and tolerates a wide breadth of biologically relevant functional groups. Mechanistic evidence supports a Heck-type mechanism, making this the first report of hydroxamate esters as electrophiles in an aza-Heck reaction and highly complementary to existing aza-Wacker technology. Further studies in our laboratory are underway to expand the scope of the reaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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31. This result also rules out C-N bond formation via a radical pathway (see reference 15e). Such a process would not be expected to be stereospecific with respect to alkene geometry. In addition, the reaction is unaffected by the addition of TEMPO, arguing against a radical-based mechanism (see the Supporting Information).
32. We have also examined the use of N-methyl, O-phenyl hydroxamates in the reaction, however, only intractable mixtures result.
33. A reviewer suggested the possibility of an alternative mechanism involving the formation of a palladium nitrene followed by [2+2] cyclization onto the alkene (see reference 34). Although we cannot rigorously exclude this based upon our current data, in considering the electronic structure of such a palladium(II) nitrene and the geometric requirements of the resulting azametallocyclobutanes in the context of the complex ring topologies reported herein, we believe that this is an unlikely possibility (see reference 35).
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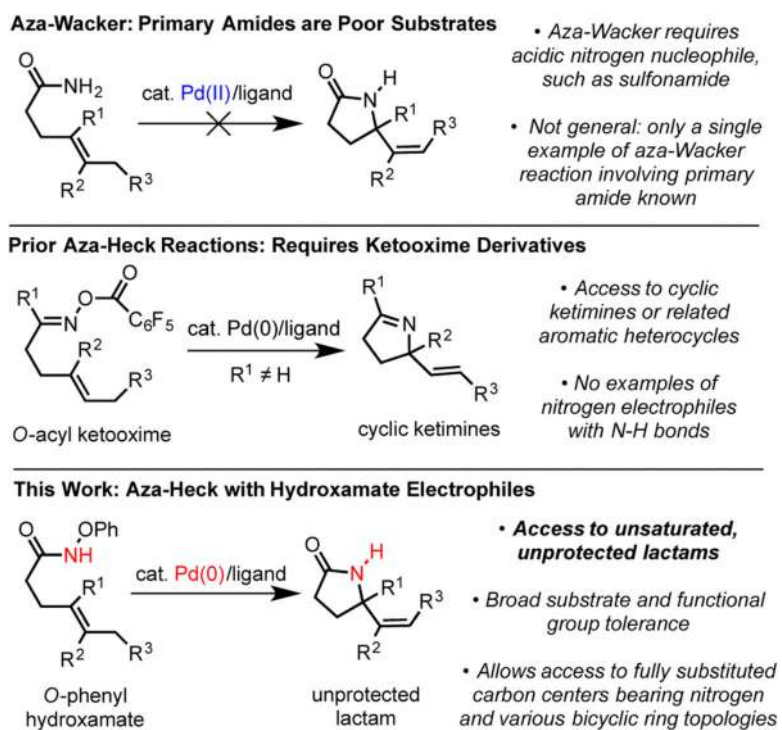
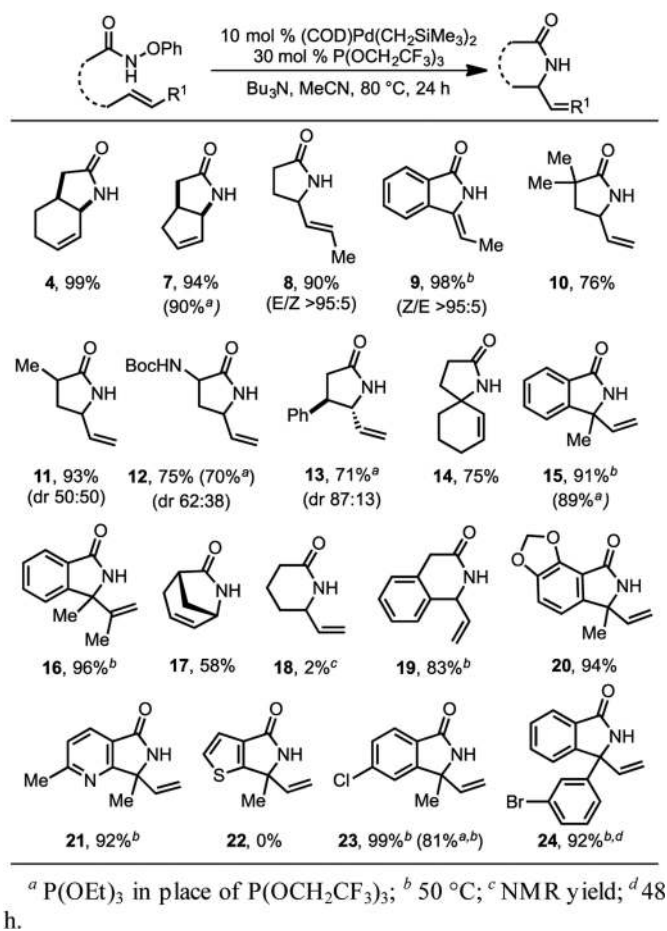
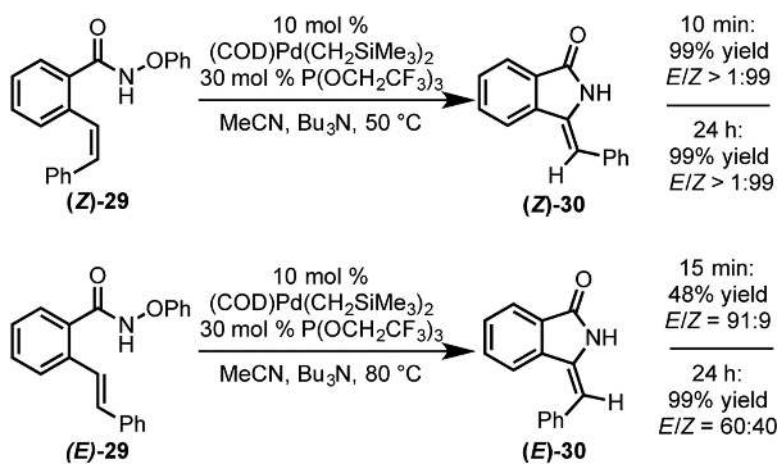


Figure 1.
Overview and context of work.



Scheme 1.
Substrate scope.



Scheme 2.
Effect of Alkene Geometry.

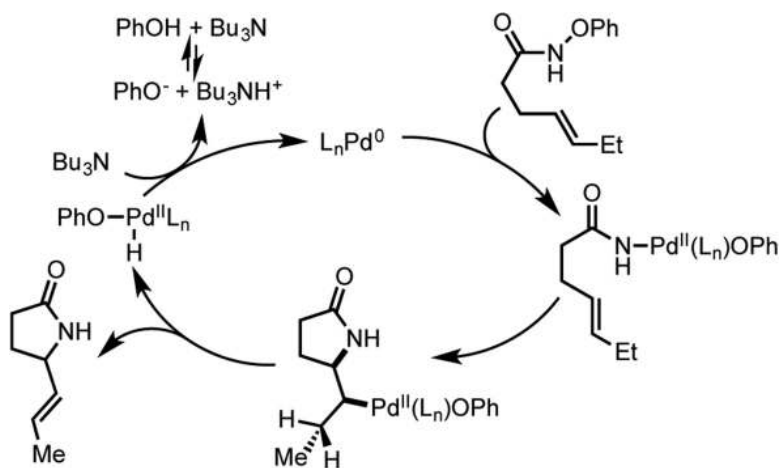
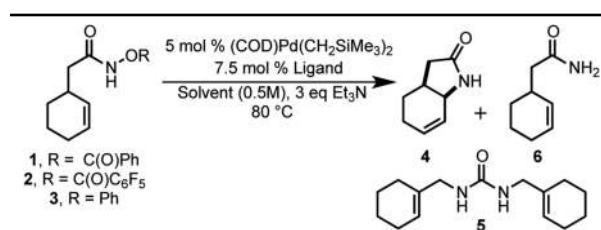


Figure 2.
Proposed aza-Heck mechanism.

Table 1

Identification of Reaction Conditions.



Entry	Substrate	Ligand	Solvent	% yield (4/5/6)
1	1	P ^t Bu ₃	DMF	0/51/1
2	2	P ^t Bu ₃	DMF	0/61/6
3	3	P ^t Bu ₃	DMF	1/0/9
4	3	PPh ₃	DMF	7/0/18
5	3	PAr ₃ ^a	DMF	13/0/16
6	3	P(OEt) ₃	DMF	12/0/2
7 ^b	3	P(OEt) ₃	MeCN	76/0/8
8 ^b	3	P(OCH ₂ CF ₃) ₃	MeCN	99/0/1

^aPAr₃ = tris(3,5-bis(trifluoromethyl)phenyl)phosphine

^b0.05 M solvent concentration, 5 eq Bu₃N, 10 mol % (COD)Pd(CH₂TMS)₂, 30 mol % ligand.