Abstract: Ligand-enabled aza-Heck cyclizations and cascades of N-(pentafluorobenzoyloxy)carbamates are described. These studies encompass the first examples of efficient non-biased 6-exo aza-Heck cyclizations. The methodology provides direct and flexible access to carbamate protected pyrrolidines and piperidines.

Pyrrolidines and piperidines are two of the most common saturated heterocycles used in pharmaceutical development (Scheme 1A). Consequently, efficient and general methods for their preparation are required. A conceptually appealing approach lies in the intramolecular aza-Wacker process, where oxidative cyclization of an NH nucleophile with an alkene occurs under PdII-catalyzed conditions (Scheme 1B). This method has been developed extensively, but, in general, still requires relatively acidic NH units, such as sulfonamides (PG = SO2R), for efficient reactivity.[2–4] Aza-Wacker cyclizations of less acidic carbamates (PG = CO2R) are much slower[3e] and are limited to 5-ring cyclizations involving more reactive classes of alkene (e.g., cyclic or sterically undemanding variants).[3c–f,4] Because carbamate protecting groups (e.g., Boc, Cbz) offer the greatest downstream flexibility, methods that can circumvent these limitations and provide direct access to protected pyrrolidines and piperidines are likely to find broad use.

A solution to the aza-Wacker “carbamate problem” potentially resides in the development of an aza-Heck process where an activated N-hydroxycarbamate unit (2) is exploited for N–O oxidative addition (to 3) prior to C–N bond forming migratory insertion of the alkene (Scheme 1C).[5] The key to this umpoled approach is that it relies on the electrophilicity of the N-center rather than on its acidity (cf. Scheme 1B), such that wide scope might be expected. Further potential benefits include: (a) direct access to the substrates by Mitsunobu alkylation of bifunctional amino reagents 1,[6] (b) the avoidance of (hazardous) external oxidants,[7] which, in turn, should allow highly tunable/stabilizing phosphine ligands to be used, (c) a compatibility with organometallic reagents in cascade processes,[8] and (d) predictable syn-amino-palladation of the alkene.[4] To date, the range of catalytically useful N–O oxidative addition processes developed is still very limited,[9,11,12] such that the viability of the approach in Scheme 1C was deemed uncertain. Nevertheless, as described below, the identification of a privileged ligand set has allowed us to achieve both the envisaged aza-Heck cyclizations, as well as related cascade processes. The new method is efficient for both 5-exo and non-biased 6-exo cyclizations; this latter aspect is particularly significant as prior aza-Heck protocols cannot achieve cyclizations of this type.[5,10–12] The end result is a highly flexible method that enables the two-step conversion of bis- or trishomoallylic alcohols to carbamate protected pyrrolidines or piperidines.

At the outset of our studies, only three principal classes of aza-Heck N–O donor were known: O–Bz ketoxime esters reported by Narasaka et al. in 1999 (Class 1),[10] O–Bz hydroxysulfonamides reported by our group in 2016 (Class 2), and O–Bz ketoxime esters reported by our group in 2016 (Class 2).
and O-phenyl hydroxamates reported by Watson and co-workers in 2016 (Class 3). Each system exhibits prescriptive ligand requirements, although, in general, electron poor P-based ligands are required for efficient reactivity. Class 1 and Class 2 N–O donors cyclize via a cationicaza-Pd\(^{II}\) intermediate, access to which is driven by facile protodecarboxylation of the pentafluorobenzoate leaving group. Given these considerations, we elected to investigate the cyclization of O\(^{3}\)Bz carbamate 2a in the presence of Pd systems modified by weak donor ligands. Gratifyingly, we found that the target cyclization was feasible, and, for this non-demanding system, a variety of triarylphosphine ligands were reasonably effective using Pd\(_3\)(dba), as the precatalyst (see the Supporting Information). Ultimately, the optimal system was PA-Ph (L-1, PA = 1,3,5,7-tetramethyl-2,4,8-trioxo-6-phosphaadamantanyl) and, using this ligand, we were able to access target 4a in 85% yield after optimization of other reaction parameters. L-1 is a bulky and electron poor ligand, with the latter fact resulting from its constrained C–P–C bond angle and inductively withdrawing oxygen atoms. The bulky tert-butyl unit of 2a is also beneficial, with less sterically demanding systems 2b and 2c cyclizing in lower but acceptable yields.

The efficacy of L-1 prompted us to undertake the one-step synthesis of a variety of electronically tuned substrates via arylation of commercially available PA-H (see the SI). These studies revealed that systems with electron withdrawing groups at the para-position of the aryl unit were especially effective, such that L-2 and L-3 emerged as complementary ligands for subsequent studies. Using this ligand set, we explored the scope of the catalyst system for 5-exo aza-Heck cyclizations and found it to be highly effective across a wide range of substrates (Table 1). Different carbamates are tolerated (4a–d), diastereoselective processes are readily achieved (4f–h), tetrasubstituted stereocenters can be constructed (4i, 4k, and 4m) and electron poor alkynes participate efficiently (2j to 4j). The method is especially powerful for bicyclic ring construction; 5-exo cyclization onto exocyclic (4k) or cyclic (4l) alkynes provided complex perhydroindole scaffolds, and spiro (4m) or transannular (4n) C–N bond formations were also efficient. For demanding systems (e.g., 4i) L-2 or L-3 provide 10–15% higher yields than L-1 (selected comparisons are given in the SI). The results in Table 1 show that the aza-Heck method offers far greater scope for 5-exo cyclizations than currently available aza-Wacker protocols.

Prior classes of aza-Heck process cannot achieve efficient 6-exo cyclizations of non-biased systems, and a solution to this issue represents a longstanding challenge of the area. We were pleased to find that the present method addresses this, as demonstrated by the cyclizations of 2o and 2p, which occurred with good levels of efficiency to afford 4o and 4p, respectively (Table 2). More highly substituted systems can also be generated (e.g., 4s and 4f), with the method offering particularly good scope for the construction of tetrahydroisoquinolines (4r and 4u), as well as unusual aza-variants (4v and 4w). The process is effective for cyclizations involving both electron rich (4r) and electron poor (e.g. 4u) alkynes. For these more demanding 6-exo cyclizations an N-Boc group is required; cyclization to afford methyl carbamate system 4q occurred in only 33% yield under optimized conditions. The use of PA-Ar ligand systems is also critical for the processes in Table 2, with L-2 or L-3 being the preferred variants. Triarylphosphines that were effective for 5-exo cyclization generated 4p in less than 10% yield (see the SI). The PA-Ar ligand system even enabled 7-exo cyclization to afford 4x, albeit in modest yield.

For the processes described here, our collective observations are supportive of an aza-Heck pathway akin to that proposed for Class 1 and Class 2 N–O donors. Under optimized conditions, cyclization of O\(^{3}\)Bz system 2k in the presence of NH system 5 provided target 4k in 79% yield and aza-Wacker product 4a was not observed (Scheme 2A). This result confirms that the N–O bond acts as an internal oxidant only. Accordingly, N–O oxidative addition to 3 should be followed by syn-stereospecific amino-palladation of the alkyne. Consistent with this, cyclization of trans-acrylate 2t delivered adduct 4t as a single geometric isomer, in which the alkene substituents that were present in the starting material are now in a cis-arrangement. The observed switch in geometry is consistent with a sequence of syn-amino-pallada- tion and syn-β-hydride elimination (Scheme 2B); a similar phenomenon is observed in the conventional Heck reaction.

For the cyclization of 2u and 2v, this geometry inversion was not observed at full conversion, with 4u and 4v formed in >25:1 Z: E ratios. However, when the cyclization of

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>4a</td>
<td>78%</td>
</tr>
<tr>
<td>4b</td>
<td>78%</td>
</tr>
<tr>
<td>4c</td>
<td>70%</td>
</tr>
<tr>
<td>4d</td>
<td>78%</td>
</tr>
<tr>
<td>4e</td>
<td>80%</td>
</tr>
<tr>
<td>4f</td>
<td>61%</td>
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<tr>
<td>4g</td>
<td>66%</td>
</tr>
<tr>
<td>4h</td>
<td>77%</td>
</tr>
<tr>
<td>4i</td>
<td>87%</td>
</tr>
<tr>
<td>4j</td>
<td>95%</td>
</tr>
<tr>
<td>4k</td>
<td>52%</td>
</tr>
<tr>
<td>4l</td>
<td>78%</td>
</tr>
<tr>
<td>4m</td>
<td>81%</td>
</tr>
<tr>
<td>4n</td>
<td>64%</td>
</tr>
</tbody>
</table>

[a] Dioxane (0.3 M) was used as solvent. Alkene geometry of substrates: 2a, E; 2b, E; 2c, E; 2d, E; 2e, 6:1 E: Z; 2f, E; 2g, E; 2h, E; 2i, Z: 2j, E; 2k, E.
2u was run to partial conversion (3 h), 4u was generated in a 4:1 E:Z ratio, such that isomerization of the initially formed product likely accounts for the geometry of isolated material (see the SI for details). As with Class 1 and 2aza-Heck processes, protodecarboxylation of the pentafluorobenzoate leaving group likely plays a key role in the processes described here. ¹³F and ¹H NMR studies revealed that this process is intimately linked to turnover; in the cyclization of CF₃-2i, CF₃-H was formed at the same rate as cyclization product CF₃-4i (Scheme 2C). Accordingly, we suggest that a cationic aza-Pd²⁺ intermediate is required for cyclization and access to this is driven by triethylammonium mediated protodecarboxylation of pentafluorobenzoate, a process that we have shown to be facile. The efficiency of the PA-Ar ligand system is consistent with studies by Hanley and Hartwig where electron poor and bulky P-based ligands were found to accelerate alkene aza-palladation in other contexts. For the current processes, the synergy of a bulky ligand system and a bulky N-protecting group may be especially beneficial, and this might account for the higher efficiencies observed for N-Boc protected systems. The conformational control that this unit provides is also likely a key factor. The aza-Heck process can also be adapted to cascade sequences where the alkyl-Pd²⁺ intermediate formed upon alkene amino-palladation is diverted to a subsequent C–C bond forming event. For example, aza-Heck–Heck cyclization of bis-alkenyl system 2y delivered spirocycle 4y in 68% yield (Scheme 3A). We have also assessed the feasibility of partially intermolecular cascade sequences as a means of providing a modular and flexible approach to alkene 1,2-carboamination (Scheme 3B). Cyclization of 6a in the presence of N-methylindole-2-boric acid pinacol ester (200 mol %) provided 1,2-amino-arylation product 7aa in 73% yield. Other electron rich heteroaryl boronic esters were also able to trap the alkyl-Pd²⁺ intermediate efficiently to give 1,2-amino-arylation products 7ab–7ad. In summary, we outline highly efficient aza-Heck cyclizations of activated N-hydroxycarbamates. The chemistry is reliant on PA-Ar ligand systems, and, importantly, these allow, for the first time, efficient non-biased 6-exo cyclizations. Further generalization of the approach, including the development of asymmetric variants and other classes of cascade reaction, will be reported in due course. In broader terms, the studies described here have uncovered a new entry to aza-Pd²⁺ intermediates via N–O oxidative addition.
[A] An intramolecular alken 1,2-carboamination reaction:

\[
\text{Boc}_2N\overset{\text{O}}{\text{O}^{\text{F}_{\text{Bz}}}}\text{2y} \xrightarrow{\text{Pd}_2(\text{dba})_2 (5 \text{ mol\%})} \text{PhN} (100 \text{ mol\%}) \text{ THF (0.4 M), } 130 ^\circ C \text{ } 4y, \text{ 68\% Yield}
\]

[B] Two component alken 1,2-aminooarylation reactions:

\[
\text{MeOCH}_2C\overset{\text{O}}{\text{F}_{\text{Bz}}} \text{6a} \xrightarrow{\text{Pd}_2(\text{dba})_2 (5 \text{ mol\%})} \text{ArBPin (200 mol\%) } \text{Et}_2\text{N (25 mol\%) } \text{PhMe (0.4 M), } 130 ^\circ C \text{ } \text{MeO}\text{N} \text{MeO} \text{MeO}
\]

\[
\text{MeOCH}_2\text{N}C \text{Ph} \text{7a, 73\% Yield (X = NMe)} \text{7b, 57\% Yield (X = O)} \text{7c, 59\% Yield (Ar = 2-thienyl)} \text{7d, 72\% Yield (X = S)}
\]

Scheme 3. Cascade processes.

The now broad utility of oxime ester derived imino-Pd\textsuperscript{II} intermediates\textsuperscript{[10,21]} application of this unusual initiation mode\textsuperscript{[9]} in the design of other redox neutral C–N bond formations can be anticipated.

Acknowledgements

We thank AstraZeneca and EPSRC (EP/M506473/1; studentship to L.R.H.), FAPESP (Grant no. 2016/00422-0; studentship to R.C.C.), and the Royal Society (URF to J.F.B.), Dr David Whittaker and Dr Michael Nunn (AstraZeneca) are thanked for assistance.

Conflict of interest

The authors declare no conflict of interest.

Keywords: aza-Heck reaction · cascade reactions · N-heterocycles · palladium

How to cite: Angew. Chem. Int. Ed. 2018, 57, 5124–5128
Angew. Chem. 2018, 130, 5218–5222


[4] Aza-Wacker processes proceed via condition dependent syn- or anti-aminopalladation pathways. The acidity of the NH unit is an important factor in the former (see Ref.\textsuperscript{[3g]}), whereas the nucleophilicity of this component is an important factor in the latter; as such, sulfonamides are more effective than carbanitrides in both scenarios. The prevalence of the competing and stereochemically divergent aminopalladation pathways impacts diastereo- and/or enantioselective processes. The SI contains a comparison of aza-Heck vs. aza-Wacker protocols for the synthesis of 4h.


[7] The avoidance of an external oxidant is beneficial for scale-up.

[8] Organometallic reagents effect reduction of Pd\textsuperscript{II} catalysts used in aza-Wacker reactions and so are not compatible with this approach. For a process that is stoichiometric in Pd\textsuperscript{II}, see: L. M. Ambrosini, T. A. Cernak, T. H. Lambert, Synthesis 2010, 870.


[16] Attempted isolation of the (E)-isomer of 4u was not possible due to facile isomerization to the (Z)-isomer during chromatography.


[18] For selected examples of Pd\textsuperscript{II}-catalyzed alkene 1,2-carboamination reactions under oxidative conditions, see: a) T. A. Cernak, T. H.


[20] In efforts towards this, we have found that 41 is generated in 44% yield and 48% ee when 1-2 is replaced by (S,R,R)-(++)-(3,5-dioxa-4-phosphacyclohepta[2,1-a:3,4-a’]dinaphthalen-4-yl)bis(1-phenylethyl)amine.


Manuscript received: January 26, 2018
Accepted manuscript online: February 28, 2018
Version of record online: March 22, 2018