Diverse N-Heterocyclic Ring Systems via Aza-Heck Cyclizations of N-(Pentafluorobenzoyloxy)sulfonamides

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Abstract: Aza-Heck cyclizations initiated by oxidative addition of Pd0-catalysts into the N–O bond of N-(pentafluorobenzoyloxy)sulfonamides are described. These studies, which encompass only the second class of aza-Heck reaction developed to date, provide direct access to diverse N-heterocyclic ring systems.

There has been a resurgence of interest in the development of processes based on the Mizoroki–Heck reaction. Notable contributions include boryl-Heck alkene functionalizations and remote relay Heck C−C bond formations. Our focus has been on the development of aza-variants of the Heck reaction, because of the importance of N-containing ring systems in drug discovery. Within this context, the Narasaka process, which involves the Pd-catalyzed cyclization of O-pentafluorobenzoyl ketoxime esters with alkenes, is unique in harnessing key steps that are analogous to the conventional Heck reaction: 1) an unusual oxidative addition into the N–O bond of 1 to afford cationic imino-Pd intermediate 2;[7,8] 2) C–N bond forming alkene migratory insertion;[9] and 3) β-hydride elimination (Scheme 1A). Imino-PdII intermediates can also be explored more widely in redox neutral processes, such as diverse alkene 1,2-carboaminations,[8] aryl C–H aminations,[7a] alkene aziridinations,[10] alkene 1,2-iodoaminations,[11] aryne aminofunctionalizations,[12] and C–C bond activations.[13]

Efforts to expand the range of redox active donors available for accessing aza-PdII intermediates led us to consider whether activated hydroxysulfonamide derivatives might be viable (Scheme 1B).[14] In this approach, N-(pentafluorobenzoyloxy)sulfonamides 4a/b, which we have found easy to prepare on gram scale,[15] act as a formal nitrene equivalent, but with key distinguishing aspects. First, as with nitrenes, 4a/b function as both a nucleophile and electrophile, but, importantly, these features are decoupled, such that their unveiling can be orchestrated in a controlled manner. Second, nucleophilic modification of 4a/b can be achieved under stereospecific Mitsunobu conditions and this allows readily available enantiopure secondary alcohols to be exploited in synthetic sequences.[16] Third, and most importantly, 5a/b do not function as an electrophile by direct reaction at nitrogen, with this reactivity facet instead controlled by the Pd-center of aza-PdII species 6a/b. Consequently, alkylated derivatives 5a/b can, in principle, be adapted to asymmetric cyclizations and cascade sequences as well as other processes typical of Pd-catalysis. Herein, we delineate preliminary studies towards this broad goal by reporting what is, to the best of our knowledge, only the second class of aza-Heck reaction developed to date (Scheme 1B, box).[19] The process provides high versatility for the synthesis of complex N-...
heterocyclic ring systems[20] and can be integrated into cascade sequences to provide alkene 1,2-carboamination products. This validates the broader N-heteroannulation strategy outlined in Scheme 1B.

Initial studies focused on aza-Heck cyclization of monosubstituted alkene 7a, which was prepared in 70% yield by Mitsunobu alkylation of 4a with pent-4-en-1-ol (Scheme 2).[15]

Under conditions related to those previously optimized for aza-Heck cyclizations of oxime esters, where P-(3,5-(CF3)2C6H3)3 was identified as a privileged ligand,[5] ketone 8a was isolated in 82% yield. 1H NMR analysis of crude reaction mixtures indicated that 8a forms via hydrolysis of initial aza-Heck product 8a.

Cyclization of 7a was considered relatively easy as both the N-O bond and alkene are sterically accessible. To integrate the new process into synthetically attractive settings we sought substrates where β-hydride elimination to form hydrolytically sensitive enamides was not possible. Accordingly we focused on cyclic alkene 7ba, which was expected to deliver bicyclic system 8b, due to the presumed mechanistic constraints of syn-αmino palladation and syn-β-hydride elimination (Table 1). In the event, this system was challenging, with initial attempts generating 8b in only 34% yield as a 3:1 mixture with regioisomer 8n (entry 1); this likely arises via Pd-hydride mediated isomerization of 8b. Inefficiencies were attributed to competing protodepalladation and β-hydride elimination at the stage of the aza-PdII intermediate; this latter pathway led to the isolation of the corresponding aldehyde.[21] Optimization was undertaken focusing on activating group, solvent, and ligand. O-Trifluoroacetyl activated variant 7bc offered marginal efficiency gains (entry 3), whereas an O-Ms activated system 7bb was less effective. Less dissociating activating groups, such as O-Bz, were completely ineffective (see below). Fortunately, it was found that solvent effects were pronounced, with n-BuCN, MeCN, and THF all promoting cyclization of 7ba to target 8b in useful yield (entries 4, 6, 7). The most efficient method used a mixed-solvent system and sub-stoichiometric quantities of Et3N (see below; entry 5). The process is highly sensitive to the nature of the phosphine ligand, and, from an exhaustive screen of commercial variants, the only other systems found to provide greater than 20% yield were PPh3, dppp, and P(4-(CF3)2C6H3)3.

The scope of the aza-Heck process is outlined in Table 2, with fine tuning of reaction solvent required on a case-by-case basis. Cyclization of 7c, which involves a cyclopentene, generated bicyclic system 8c in high yield and as a single diastereomer. Efficient cyclizations were observed for processes involving 1,2-disubstituted alkenes. For example, 7d delivered 8d in 81% yield and with complete selectivity over the corresponding enamide (cf. 7a to 8a). 1,1-Disubstituted alkenes are also tolerated, albeit with greater variation in efficiency. Cyclization of 7f generated the challenging tetrasubstituted stereocenter of pyrrolidine 8f in 80% yield. More sterically demanding systems 7g and 7h were less effective, but still delivered targets 8g and 8h in workable yields. Systems with substitution on the alkene tether can provide diastereo-selective processes. For example, 7k generated cis-2,5-disubstituted pyrrolidine 8k in 58% yield and more than 10:1 d.r.; for this process, an N-tosyl protecting group was less effective.[13] Similar efficiencies were observed for 7j, 7l, and 7m, with the latter affording complex 2,2,5-trisubstituted pyrrolidine 8m in high diastereoselectivity. Electron-deficient alkenes also participate: cyclization of acrylate 7n provided 8n in 78% yield, thereby validating a novel entry to versatile alkylidene pyrrolidines.

The chemistry can be used to provide challenging bridged ring systems common to many alkaloid targets (Scheme 3). For example, cyclization of 7a, which involves a cycloheptene constructed by RCM,[15] provided tropane 8o in 60% yield; this is the core structure of multiple natural products including cocaine.[22] Alternatively, cyclization of 7p generated regioisomeric 6-azabicyclo[3.2.1]octene scaffold 8p in 76% yield.[23] The structures of 8o and 8p were confirmed by X-ray diffraction.[15]

Preliminary studies show that the chemistry will be of utility in other contexts. All aza-Heck processes described so far involve 5-exo cyclization; however, even at the present level of development, 6-exo cyclization is possible (Scheme 4A). Indeed, exposure of styrnyl system 7q to optimized conditions provided tetrahydroisooquinolines.

Table 1: Optimization of a demanding cyclization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Ligand</th>
<th>Solvent</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>T (°C)</th>
<th>Yield [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bz</td>
<td>P(3,5-(CF3)2C6H3)3</td>
<td>DMF</td>
<td>4</td>
<td>15</td>
<td>400</td>
<td>80</td>
<td>34 (3:1)</td>
</tr>
<tr>
<td>2</td>
<td>Ms</td>
<td>P(3,5-(CF3)2C6H3)3</td>
<td>DMF</td>
<td>4</td>
<td>15</td>
<td>400</td>
<td>80</td>
<td>4 (n.d.)</td>
</tr>
<tr>
<td>3</td>
<td>(CO)CF3</td>
<td>P(3,5-(CF3)2C6H3)3</td>
<td>DMF</td>
<td>5</td>
<td>20</td>
<td>200</td>
<td>80</td>
<td>46 (3:1)</td>
</tr>
<tr>
<td>4</td>
<td>Bz</td>
<td>P(3,5-(CF3)2C6H3)3</td>
<td>n-BuCN</td>
<td>2.5</td>
<td>12.5</td>
<td>50</td>
<td>110</td>
<td>80 (17:1)</td>
</tr>
<tr>
<td>5</td>
<td>Bz</td>
<td>P(3,5-(CF3)2C6H3)3</td>
<td>n-BuCN/DMF(6:1)</td>
<td>2.5</td>
<td>12.5</td>
<td>50</td>
<td>110</td>
<td>91 (12:1)</td>
</tr>
<tr>
<td>6</td>
<td>Bz</td>
<td>P(3,5-(CF3)2C6H3)3</td>
<td>MeCN</td>
<td>5</td>
<td>20</td>
<td>100</td>
<td>100</td>
<td>76 (3:1)</td>
</tr>
<tr>
<td>7</td>
<td>Bz</td>
<td>P(3,5-(CF3)2C6H3)3</td>
<td>THF</td>
<td>5</td>
<td>20</td>
<td>100</td>
<td>100</td>
<td>62 (1:0)</td>
</tr>
<tr>
<td>8</td>
<td>Bz</td>
<td>P(3,5-(CF3)2C6H3)3</td>
<td>n-BuCN</td>
<td>5</td>
<td>20</td>
<td>100</td>
<td>100</td>
<td>77 (24:1)</td>
</tr>
<tr>
<td>9</td>
<td>Bz</td>
<td>PPh3</td>
<td>n-BuCN</td>
<td>5</td>
<td>20</td>
<td>100</td>
<td>100</td>
<td>51 (13:1)</td>
</tr>
<tr>
<td>10</td>
<td>Bz</td>
<td>dppp</td>
<td>n-BuCN</td>
<td>5</td>
<td>10</td>
<td>100</td>
<td>110</td>
<td>24 (12:1)</td>
</tr>
<tr>
<td>11</td>
<td>Bz</td>
<td>P(4-(CF3)2C6H3)3</td>
<td>n-BuCN</td>
<td>5</td>
<td>20</td>
<td>100</td>
<td>100</td>
<td>33 (3:1)</td>
</tr>
</tbody>
</table>

[a] In situ yield; 8b:iso-8b ratio is given in parentheses.

These are not the final page numbers!
We have also assessed the possibility of alkene 1,2-carboamination processes by trapping the alkyl-PdII intermediate generated after migratory insertion (Scheme 4B). Exposure of \( \textbf{7r} \) to aza-Heck conditions afforded bicycle \( \textbf{8r} \) in 86% yield, via Heck trapping of \( \textbf{7r}' \). The development of further alkene aza-functionalizations will be a focus of future work.

The mechanism of the aza-Heck processes is likely akin to that of the Narasaka cyclization of O-pentafluorobenzoyl ketoxime esters (Scheme 5, \( \textbf{7d} \) to \( \textbf{8d} \)).[5,8] Pd\( ^{0} \)L (L = P-(3,5-(CF\(_{3}\))\(_{2}\)C\(_{6}\)H\(_{3}\))\(_{3}\)) generated in situ effects N-O oxidative addition of \( \textbf{7d} \) to provide \( \textbf{I} \); despite extensive efforts, we have so far been unable to isolate aza-PdII intermediates related to \( \textbf{I} \). Efficient aza-Heck cyclization requires dissociation of pentafluorobenzoate from \( \textbf{I} \) to access cationic intermediate \( \textbf{II} \).[8] This assertion is based on the observation that less dissociating leaving groups (for example, O-Bz) are ineffective, and chloride additives (for example, \( n\)-Bu\(_{4}\)NCl) com-

**Table 2: Scope of the aza-Heck process.**

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Product</th>
<th>Starting material</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \textbf{7c} ) (( n)-BuCN)</td>
<td>( \textbf{8c} )</td>
<td>91% Yield (20:1 d.r.)</td>
<td>8d</td>
</tr>
<tr>
<td>( \textbf{7a} ) (( n)-BuCN)</td>
<td>( \textbf{8a} )</td>
<td>77% Yield</td>
<td>8f</td>
</tr>
<tr>
<td>( \textbf{7g} ) (6:1 n-BuCN:DMF)</td>
<td>( \textbf{8g} )</td>
<td>42% Yield (2:1 d.r.)</td>
<td>8h</td>
</tr>
<tr>
<td>( \textbf{7i} ) (( n)-BuCN)</td>
<td>( \textbf{8i} )</td>
<td>81% Yield (2:1 d.r.)</td>
<td>7l</td>
</tr>
<tr>
<td>( \textbf{7k} ) (6:1 n-BuCN:DMF)</td>
<td>( \textbf{8k} )</td>
<td>58% Yield (10:1 d.r.)</td>
<td>7l (PhMe)</td>
</tr>
<tr>
<td>( \textbf{7m} ) (PhMe)</td>
<td>( \textbf{8m} )</td>
<td>64% Yield (10:1 d.r.)</td>
<td>7n (6:1 n-BuCN:DMF)</td>
</tr>
<tr>
<td>( \textbf{7o} )</td>
<td>( \textbf{8o} )</td>
<td>60% Yield</td>
<td>( \textbf{7p} )</td>
</tr>
</tbody>
</table>

[a] Reaction solvent is specified in parentheses under each starting material. Full details are given in the Supporting Information.

**Scheme 3.** Bridged ring systems by aza-Heck cyclization.

**Scheme 4.** Examples of further reactivity.

**Scheme 5.** Preliminary mechanism based on observations from current and previous work.
pletely suppress cyclization; in both cases protodepalladation to the corresponding sulfonamide predominates. From II, syn-migratory insertion of the alkene generates alkyl-Pd intermediate III. The intermediacy of III is corroborated by the cyclization of 7r to 8r, while support for the feasibility of syn-stereospecific alkene migratory insertion is found in studies on aza-Wacker cyclizations.[24,25] From III, β-hydride elimination releases the product (8d) and Pd^0-hydride IV, which undergoes base (Et_3N) induced reductive elimination to close the catalytic cycle. The equilibrium between neutral and cationic complexes I and II is shifted forward by triethylammonium mediated protodecarboxylation of the otherwise inhibitory pentafluorobenzoate leaving group. We have previously shown that this process is rapid,[8] and 3^19F NMR analysis of crude reaction mixtures has confirmed that it is operative in the current scenario. This also accounts for the use of sub-stoichiometric (catalytic) quantities of Et_3N under optimized conditions.

It is pertinent to comment on the synthetic scope of the prototype 5-exo aza-Heck processes outlined here versus complementary 5-exo aza-Wacker cyclizations of alkyl NH-sulfonamides, which require an external oxidant (for example, air or oxygen).[24] Despite extensive development, this latter method still has key limitations: for example, cyclization of systems with large α-substituents (larger than methyl) have not been achieved (cf. 7j-m), hindered acyclic olefins do not participate (cf. 7b), and electron-deficient alkynes cannot be used due to competing conjugate addition (cf. 7n). Additionally, aza-Heck cyclization seems uniquely suited to demanding systems (Scheme 3) and cascade polycyclizations (Scheme 4B). Earlier work using oxime esters has also established N-O oxidative addition as a unified platform for the design of diverse redox-neutral alkene 1,2-carboamination processes that cannot be achieved using an aza-Wacker approach.[26] From a practical viewpoint, a pre-installed internal oxidant may be preferable for scale-up or redox sensitive substrates. From a practical viewpoint, a pre-installed internal oxidant may be preferable for scale-up or redox sensitive substrates. Importantly, this unit can be brought in directly by Mitsunobu oxidation of sub-stoichiometric (catalytic) quantities of Et_3N under optimized conditions.

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

15. Details are given in the Supporting Information. CCDC 1482096 (7ba), 1482097 (8o), and 1482098 (8p) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.
16. A study on the stereospecificity of this process is given in the Supporting Information.
[17] We have demonstrated the feasibility of asymmetric Narasaka–Heck cyclizations (see Ref. [5c]). An optimized system will be reported in due course.
[18] Redox active nitrogen donors provide high flexibility for cascade design (see Ref. [8]).
[20] The Narasaka–Heck reaction is limited to cyclizations that generate initially ketimines.
[25] Addition of TEMPO to cyclizations of 7c and 7d did not result in any TEMPO trapping products, with 8c and 8d formed in yields similar to those reported in Table 2 (see Ref. [5d]).

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