



Hazelden, I., Ma, X-F., Langer, T., & Bower, J. (2016). Diverse N-heterocyclic ring systems via aza-Heck cyclizations of N-(pentafluorobenzoyloxy)sulfonamides. *Angewandte Chemie International Edition*, 55(37), 11198-11202. DOI: 10.1002/anie.201605152

Publisher's PDF, also known as Version of record

License (if available):
CC BY

Link to published version (if available):
[10.1002/anie.201605152](https://doi.org/10.1002/anie.201605152)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the final published version of the article (version of record). It first appeared online via Wiley at <http://dx.doi.org/10.1002/anie.201605152>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/pure/about/ebr-terms.html>

N-Heterocycles

International Edition: DOI: 10.1002/anie.201605152
German Edition: DOI: 10.1002/ange.201605152

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

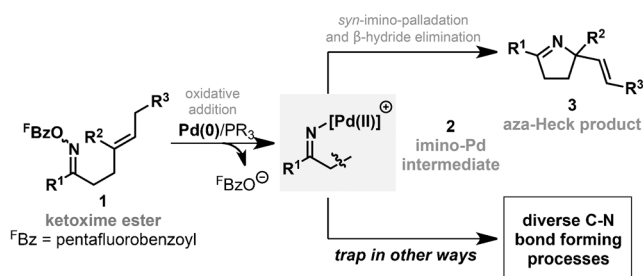
Ian R. Hazelden[†], Xiaofeng Ma[†], Thomas Langer, and John F. Bower*

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.

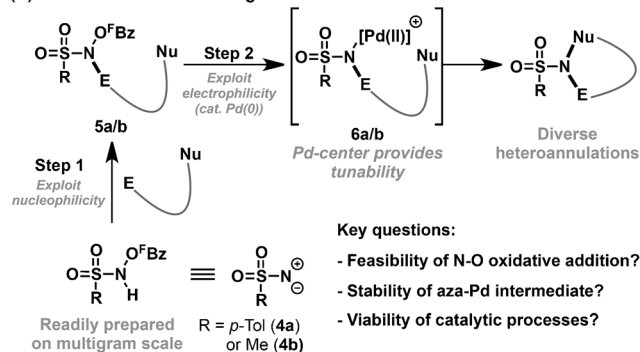
There has been a resurgence of interest in the development of processes based on the Mizoroki–Heck reaction.^[1] Notable contributions include boryl–Heck alkene functionalizations^[2] and remote redox relay Heck C–C bond formations.^[3] Our focus has been on the development of aza-variants of the Heck reaction, because of the importance of N-containing ring systems in drug discovery.^[4–7] Within this context, the Narasaka process,^[4] 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 1 A). Imino-Pd^{II} intermediates **2** can also be exploited 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-Pd^{II} intermediates led us to consider whether activated hydroxysulfonamide derivatives might be viable (Scheme 1 B).^[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,

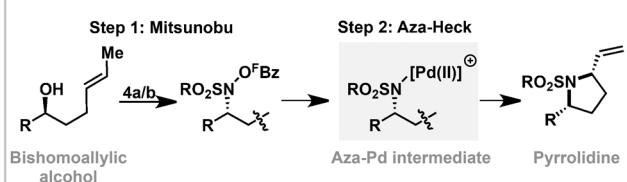
(A) The Narasaka-Heck reaction and utility of imino-Pd intermediates:



(B) Aza-Pd intermediates using other redox active N-donors?



Prototype application (this work):



Scheme 1. Aza-Pd intermediates via redox-active N-donors.

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-Pd^{II} species **6a/b**. Consequently, alkylated derivatives **5a/b** can, in principle, be adapted to asymmetric cyclizations^[17] and cascade sequences,^[18] 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 1 B, box).^[19] The process provides high versatility for the synthesis of complex N-

[*] I. R. Hazelden,^[†] Dr. X. Ma,^[†] Dr. J. F. Bower
School of Chemistry, University of Bristol
Bristol, BS8 1TS (UK)
E-mail: john.bower@bris.ac.uk

Dr. T. Langer
Pharmaceutical Technology & Development, AstraZeneca
Charter Way, Macclesfield, SK10 2NA (UK)

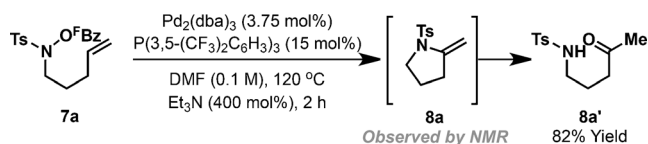
[†] These authors contributed equally.

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under <http://dx.doi.org/10.1002/anie.201605152>.

© 2016 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

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 1 B.

Initial studies focused on aza-Heck cyclization of mono-substituted alkene **7a**, which was prepared in 70% yield by Mitsunobu alkylation of **4a** with pent-4-enol (Scheme 2).^[15]



Scheme 2. A feasibility experiment.

Under conditions related to those previously optimized for aza-Heck cyclizations of oxime esters, where $\text{P}(\text{3,5-(CF}_3)_2\text{C}_6\text{H}_3)_3$ was identified as a privileged ligand,^[5] ketone **8a'** was isolated in 82% yield. $^1\text{H NMR}$ 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*-amino 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 *iso*-**8b** (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-Pd^{II} 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 acti-

Table 1: Optimization of a demanding cyclization.

Reaction scheme for Table 1: $\text{Pd}_2(\text{dba})_3$ (X mol%), Ligand (Y mol%), Solvent (0.1 M), Temp., Et_3N (Z mol%), 10–24 h.

Entry	R	Ligand	Solvent	X	Y	Z	T [°C]	Yield [%] ^[a]
1	^F Bz	$\text{P}(\text{3,5-(CF}_3)_2\text{C}_6\text{H}_3)_3$	DMF	4	15	400	80	34 (3:1)
2	Ms	$\text{P}(\text{3,5-(CF}_3)_2\text{C}_6\text{H}_3)_3$	DMF	4	15	400	80	4 (n.d.)
3	(CO)CF ₃	$\text{P}(\text{3,5-(CF}_3)_2\text{C}_6\text{H}_3)_3$	DMF	5	20	200	80	46 (3:1)
4	^F Bz	$\text{P}(\text{3,5-(CF}_3)_2\text{C}_6\text{H}_3)_3$	<i>n</i> -BuCN	2.5	12.5	50	110	80 (17:1)
5	^F Bz	$\text{P}(\text{3,5-(CF}_3)_2\text{C}_6\text{H}_3)_3$	<i>n</i> -BuCN/DMF (6:1)	2.5	12.5	50	110	91 (12:1)
6	^F Bz	$\text{P}(\text{3,5-(CF}_3)_2\text{C}_6\text{H}_3)_3$	MeCN	5	20	100	100	76 (3:1)
7	^F Bz	$\text{P}(\text{3,5-(CF}_3)_2\text{C}_6\text{H}_3)_3$	THF	5	20	100	100	62 (1:0)
8	^F Bz	$\text{P}(\text{3,5-(CF}_3)_2\text{C}_6\text{H}_3)_3$	<i>n</i> -BuCN	5	20	100	110	77 (24:1)
9	^F Bz	PPh_3	<i>n</i> -BuCN	5	20	100	110	51 (13:1)
10	^F Bz	dppp	<i>n</i> -BuCN	5	10	100	110	24 (12:1)
11	^F Bz	$\text{P}(\text{4-(CF}_3)_3\text{C}_6\text{H}_4)_3$	<i>n</i> -BuCN	5	20	100	110	33 (3:1)

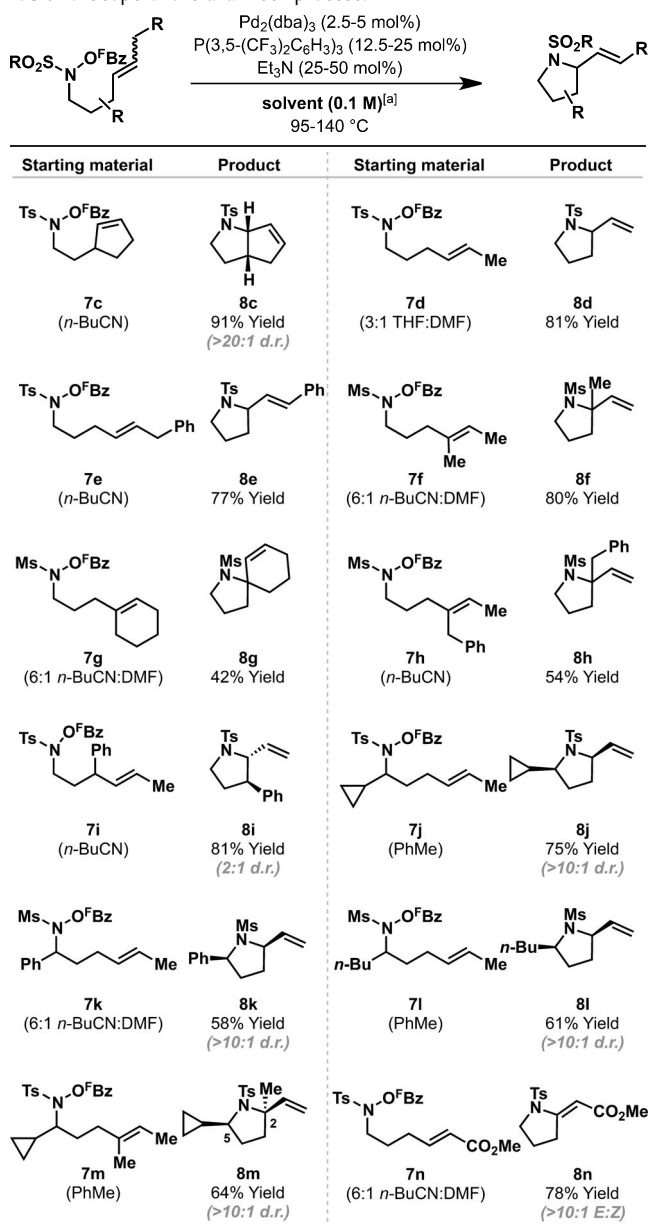
[a] In situ yield; **8b**:*iso*-**8b** ratio is given in parentheses.

ated 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 Et_3N (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 PPh_3 , dppp, and $\text{P}(\text{4-(CF}_3)_3\text{C}_6\text{H}_4)_3$.

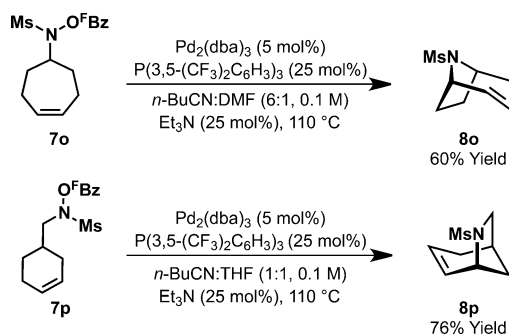
The scope of the aza-Heck process is outlined in Table 2, with fine tuning of reaction solvent required on a case-by-case basis. Cyclization of **7c**, which involves a cyclopentene, generated bicyclic system **8c** in high yield and as a single diastereomer. Efficient cyclizations were observed for 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 diastereoselective 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.^[15] 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 **7o**, 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]

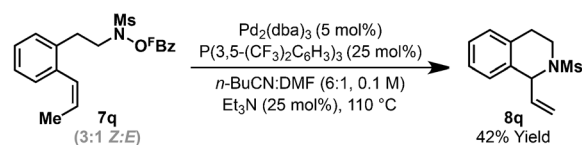
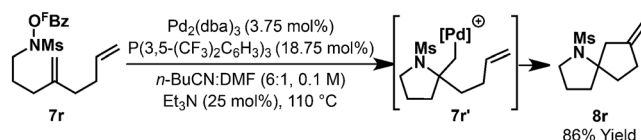
Preliminary studies show that the chemistry will be of utility in other contexts. All aza-Heck processes described so far involve 5-*exo* cyclization; however, even at the present level of development, 6-*exo* cyclization is possible (Scheme 4A). Indeed, exposure of styrenyl system **7q** to optimized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

Table 2: Scope of the aza-Heck process.

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

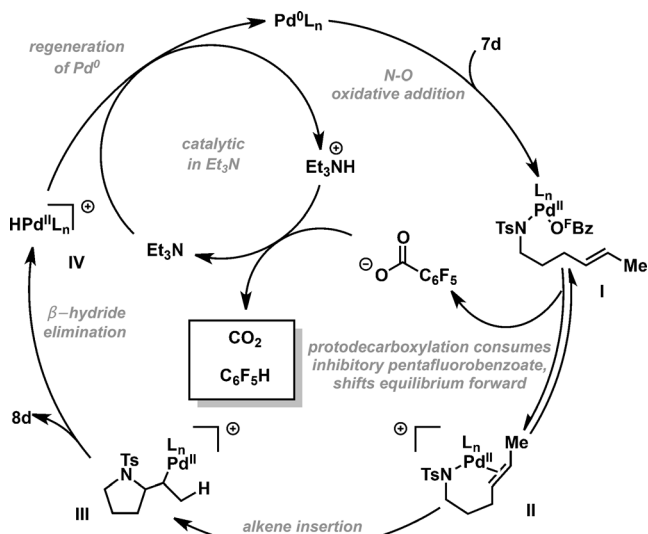
**Scheme 3.** Bridged ring systems by aza-Heck cyclization.

noline **8q** in 42% yield. We have also assessed the possibility of alkene 1,2-carboamination processes by trapping the alkyl-Pd^{II} intermediate generated after migratory insertion (Scheme 4B). Exposure of **7r** to aza-Heck conditions afforded

(A) Benzofused systems by 6-exo aza-Heck cyclization:**(B) Polycyclic systems by cascade aza-Heck cyclization:****Scheme 4.** Examples of further reactivity.

bicycle **8r** in 86% yield, via Heck trapping of **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, **7d** to **8d**).^[5,8] Pd⁰L_n (L = P-(3,5-(CF₃)₂C₆H₃)₃) generated in situ effects N-O oxidative

**Scheme 5.** Preliminary mechanism based on observations from current and previous work.

addition of **7d** to provide **I**; despite extensive efforts, we have so far been unable to isolate aza-Pd^{II} intermediates related to **I**. Efficient aza-Heck cyclization requires dissociation of pentafluorobenzoate from **I** to access cationic intermediate **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*-Bu₄NCl) com-

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^{II}-hydride **IV**, which undergoes base (Et₃N) 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 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 Et₃N 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 alkenyl 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. **7h**), and electron-deficient alkenes 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.^[8] 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 reaction of **4a/b**, enabling a two-step conversion of (enantiopure) alcohols to heterocyclic targets. Alkenyl NH-sulfonamides required for aza-Wacker cyclization are not usually prepared directly from the alcohol because the requisite primary sulfonamides do not engage efficiently in conventional Mitsunobu reactions.^[26] Further potential advantages of the aza-Heck approach are that highly tunable phosphine ligands can be used (because oxidative conditions are avoided) and predictable *syn*-migratory insertion of the alkene can be expected.^[24c]

In summary, we report aza-Heck cyclizations initiated by oxidative addition of Pd⁰-catalysts into the N–O bond of *N*-(pentafluorobenzoyloxy)sulfonamides. These studies provide direct access to *N*-heterocyclic ring systems that are not accessible using the Narasaka aza-Heck procedure.^[20] The approach exploits stepwise unveiling of the nitrenoid character embedded within *N*-(pentafluorobenzoyloxy)sulfonamide reagents. Sequential nucleophilic-electrophilic C–N bond forming strategies of this type, which involve the intermediacy of a tunable aza-Pd^{II} intermediate, should enable a wide array of *N*-heteroannulation processes. By analogy to the utility of oxime ester derived imino-Pd intermediates (**2**),^[4,5,8–13] we

also anticipate that the catalysis platform outlined here, which involves a rare example of oxidative addition of Pd⁰ into an N–O bond,^[7] should find broad applicability in the design of redox neutral C–N bond forming methods outside the immediate area of *N*-heterocyclic chemistry.

Acknowledgements

We acknowledge the European Research Council for support via the EU's H2020 Program (grant no. 639594 CatHet), AstraZeneca and EPSRC (EP/M506473/1) for a studentship (I.R.H.), and the Royal Society for a University Research Fellowship (J.F.B.).

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

- [1] *The Mizoroki-Heck Reaction* (Ed.: M. Oestreich), Wiley, Chichester, **2009**.
- [2] W. B. Reid, J. J. Spillane, S. B. Krause, D. A. Watson, *J. Am. Chem. Soc.* **2016**, *138*, 5539.
- [3] H. H. Patel, M. S. Sigman, *J. Am. Chem. Soc.* **2015**, *137*, 3462.
- [4] a) H. Tsutsui, K. Narasaka, *Chem. Lett.* **1999**, *28*, 45. Reviews: b) M. Kitamura, K. Narasaka, *Chem. Rec.* **2002**, *2*, 268.
- [5] a) A. Faulkner, J. F. Bower, *Angew. Chem. Int. Ed.* **2012**, *51*, 1675; *Angew. Chem.* **2012**, *124*, 1707; b) N. J. Race, J. F. Bower, *Org. Lett.* **2013**, *15*, 4616; c) A. Faulkner, J. S. Scott, J. F. Bower, *Chem. Commun.* **2013**, *49*, 1521; d) N. J. Race, A. Faulkner, M. H. Shaw, J. F. Bower, *Chem. Sci.* **2016**, *7*, 1508.
- [6] For a Cu-catalyzed variant, see: A. Faulkner, N. J. Race, J. F. Bower, *Chem. Sci.* **2014**, *5*, 2416.
- [7] a) Y. Tan, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 3676; b) W. P. Hong, A. V. Iosub, S. S. Stahl, *J. Am. Chem. Soc.* **2013**, *135*, 13664; for a process where *N*-O oxidative addition of Pd⁰ is invoked but not confirmed, see: c) J. He, T. Shigenari, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2015**, *54*, 6545; *Angew. Chem.* **2015**, *127*, 6645.
- [8] A. Faulkner, J. S. Scott, J. F. Bower, *J. Am. Chem. Soc.* **2015**, *137*, 7224.
- [9] For migratory insertion of alkenes into *N*-Pd bonds, see: P. S. Hanley, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2013**, *52*, 8510; *Angew. Chem.* **2013**, *125*, 8668.
- [10] K. Okamoto, T. Oda, S. Kohigashi, K. Ohe, *Angew. Chem. Int. Ed.* **2011**, *50*, 11470; *Angew. Chem.* **2011**, *123*, 11672.
- [11] C. Chen, L. Hou, M. Cheng, J. Su, X. Tong, *Angew. Chem. Int. Ed.* **2015**, *54*, 3092; *Angew. Chem.* **2015**, *127*, 3135.
- [12] T. Gerfaut, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed.* **2009**, *48*, 572; *Angew. Chem.* **2009**, *121*, 580.
- [13] T. Nishimura, S. Uemura, *J. Am. Chem. Soc.* **2000**, *122*, 12049.
- [14] For Cu-catalyzed radical cyclizations of activated hydroxysulfonamides with alkenes, see: W.-M. Liu, Z.-H. Liu, W.-W. Cheong, L.-Y. T. Priscilla, Y. Li, K. Narasaka, *Bull. Korean Chem. Soc.* **2010**, *31*, 563.
- [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]).
- [19] We use the term “aza-Heck” to describe a Pd-catalyzed process that encompasses steps analogous to the conventional Heck reaction: a) oxidative initiation at nitrogen, b) C–N forming alkene migratory insertion, and c) β -hydride elimination. “Aza-Heck” cyclizations of *N*-chloroamines have been reported but do not generate alkene products; see: a) J. Helaja, R. Göttlich, *Chem. Commun.* **2002**, 720; b) G. Heuger, S. Kalsow, R. Göttlich, *Eur. J. Org. Chem.* **2002**, 1848.
- [20] The Narasaka–Heck reaction is limited to cyclizations that generate initially ketimines.
- [21] The aldehyde likely forms via hydrolysis of an intermediate *N*-tosyl aldimine.
- [22] A. J. Humphrey, D. O’Hagan, *Nat. Prod. Rep.* **2001**, 18, 494.
- [23] M. Betou, L. Male, J. W. Steed, R. S. Grainger, *Chem. Eur. J.* **2014**, 20, 6505.
- [24] For selected methods, see: a) M. Rönn, J.-E. Backväll, P. G. Andersson, *Tetrahedron Lett.* **1995**, 36, 7749; b) R. I. McDonald, P. B. White, A. B. Weinstein, C. P. Tam, S. S. Stahl, *Org. Lett.* **2011**, 13, 2830; c) Aza-Wacker cyclizations proceed via condition-dependent *syn*- or *anti*-amino-palladation pathways; see: G. Liu, S. S. Stahl, *J. Am. Chem. Soc.* **2007**, 129, 6328; d) Review: R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, 111, 2981.
- [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]).
- [26] J. R. Henry, L. R. Marcin, M. C. McIntosh, P. M. Scola, G. D. Harris, Jr., S. M. Weinreb, *Tetrahedron Lett.* **1989**, 30, 5709.

Received: May 26, 2016

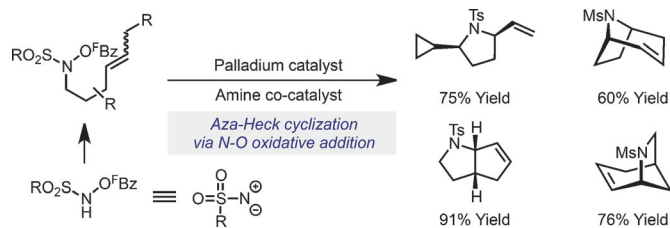
Published online: ■ ■ ■ ■, ■ ■ ■ ■

Communications



N-Heterocycles

I. R. Hazelden, X. Ma, T. Langer,

J. F. Bower*     Diverse N-Heterocyclic Ring Systems via
Aza-Heck Cyclizations of N-
(Pentafluorobenzoyloxy)sulfonamides

Aza-Heck cyclizations initiated by oxidative addition of Pd⁰ catalysts into the N–O bond of N-(pentafluorobenzoyloxy)sulfonamides are described. These studies, which are only the second class of

aza-Heck reaction developed to date, provide direct access to diverse N-heterocyclic ring systems (18 examples, 42–91% yield).