Nitrogen Heterocycles

International Edition: DOI: 10.1002/anie.201703967
German Edition: DOI: 10.1002/ange.201703967

Synthesis of [5,6]-Bicyclic Heterocycles with a Ring-Junction Nitrogen Atom: Rhodium(III)-Catalyzed C–H Functionalization of Alkenyl Azoles

*Kim Søholm Halskov, Howard S. Roth, and Jonathan A. Ellman**

Abstract: *The first syntheses of privileged [5,6]-bicyclic heterocycles, with ring-junction nitrogen atoms, by transition metal catalyzed C–H functionalization of C-alkenyl azoles is disclosed. Several reactions are applied to alkenyl imidazoles, pyrazoles, and triazoles to provide products with nitrogen incorporated at different sites. Alkyne and diazoketone coupling partners give azolopyridines with various substitution patterns. In addition, 1,4,2-dioxazolone coupling partners yield azolopyrimidines. Furthermore, the mechanisms for the reactions are discussed and the utility of the developed approach is demonstrated by iterative application of C–H functionalization for the rapid synthesis of a patented drug candidate.*

Perhaps as a result of their electronic and shape complementarity to the adenine and guanine nucleobases, [5,6]-bicyclic heterocycles with a ring-junction nitrogen atom have become increasingly prominent in medicinal chemistry, as exemplified by clinical candidates such as filgotinib, volitinib, and dinaciclib, as well as the FDA-approved drugs zolpidem, trazodone, ibudilast, ponatinib, and zaleplon.[1] Transition metal catalyzed chelation-assisted aromatic and, to a lesser extent, alkenyl, C(sp^2)–H activation and annulation has enabled the convergent synthesis of diverse heterocyclic compounds.[2] However, despite their pharmaceutical importance, only a narrow subset of [5,6]-bicyclic heterocycles with a ring-junction nitrogen atom have been assembled by this approach, specifically with the rhodium(III)-catalyzed annulation of N-vinyl imidazoles and alkynes (Figure 1 a).[3,4]

Herein we describe general methods for the rhodium(III)-catalyzed alkenyl C(sp^2)–H functionalization of C-alkenyl azoles for the synthesis of fused [5,6]-bicyclic heterocycles which incorporate from two to four nitrogen atoms (Figure 1 b,c). While previous reports have demonstrated C–H functionalization of C-aryl azoles for the synthesis of tricyclic and higher-order heterocycles,[5] to the best of our knowledge, this study represents the first investigation of C-alkenyl azole substrates.[6] These transformations are effective for alkenyl imidazoles, pyrazoles, and triazoles incorporating a variety of substitution patterns on both the alkene and the azole. With alkyne or diazoketone coupling partners, azolopyridines are obtained (Figure 1 b), while dioxazolones give azolopyrimidines (Figure 1 c).

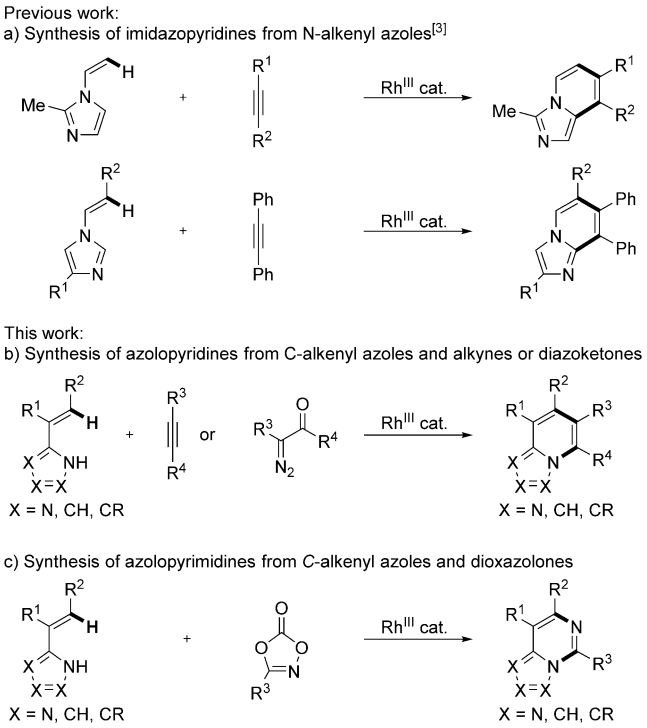
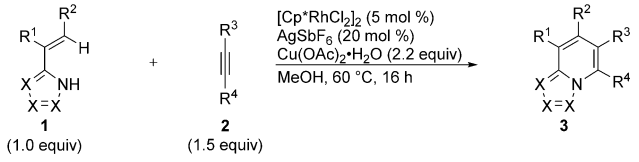


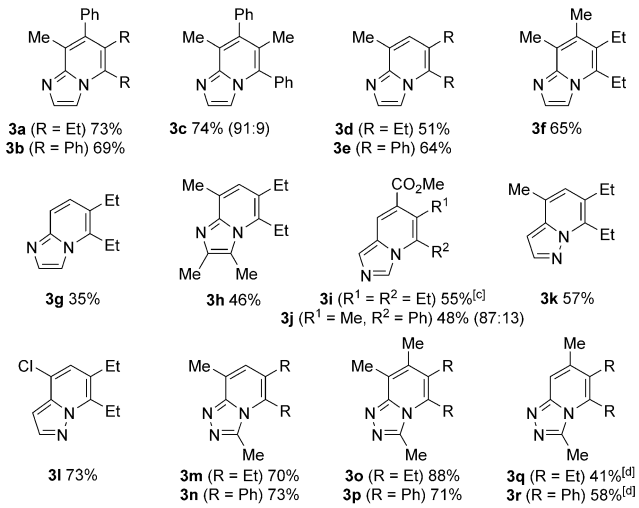
Figure 1. Synthesis of fused [5,6]-bicyclic nitrogen heterocycles by rhodium(III)-catalyzed C–H functionalization.

Upon identifying optimal reaction conditions for the annulation of C-alkenyl azoles and alkynes (see Table S1 in the Supporting Information), the reactivities of a variety of alkenyl azole and alkyne substrates were evaluated (Table 1). Both alkyl- and aryl-substituted alkynes coupled with a C2 trisubstituted alkenyl imidazole in good yields to give the imidazopyridines **3a** and **3b**, respectively. In addition, reaction of nonsymmetric 1-phenyl-1-propyne gave the product **3c** with high regioselectivity. Imidazole substrates lacking a β-substituent on the alkene (**3d** and **3e**) and with a β-methyl group (**3f**) were all effective coupling partners, while a C-vinyl imidazole coupled in a more modest yield (**3g**). As illustrated with **3h**, substitution on the imidazole ring was also tolerated. The reaction of alternative alkenyl diazoles was also investigated. Methyl urocanate, with an alkene at the 4-position of the imidazole, reacted with 3-hexyne to give **3i**, and reaction with 1-phenyl-1-propyne yielded **3j** with high regioselectivity. Moreover, an alkenyl pyrazole was a compe-

[*] Dr. K. S. Halskov, Dr. H. S. Roth, Prof. Dr. J. A. Ellman
Department of Chemistry, Yale University
225 Prospect St., New Haven, CT 06520 (USA)
E-mail: jonathan.ellman@yale.edu
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201703967.

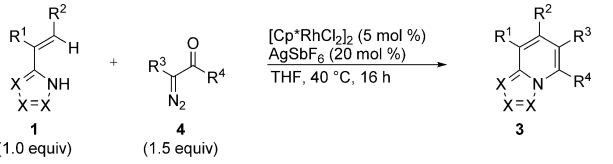
Table 1: Rhodium(III)-catalyzed C–H functionalization of alkenyl azoles with alkynes.[a,b]

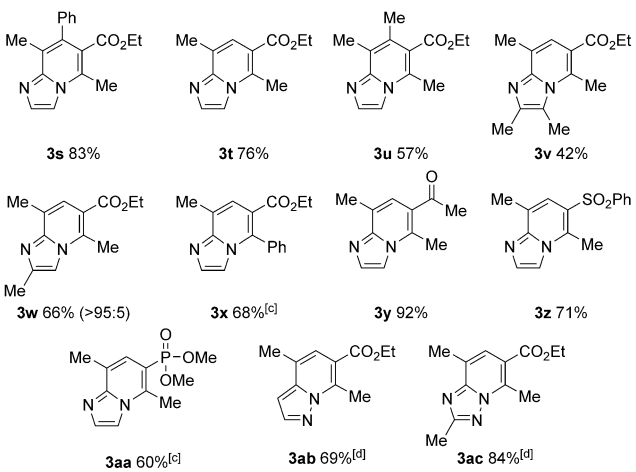




[a] Reaction conditions: **1** (0.50 mmol), **2** (1.5 equiv), 0.1 M, 16 h. [b] Yield of isolated products after chromatography on silica. [c] 3.0 equiv **2**. [d] 100 °C. Cp* = C_5Me_5.

Table 2: Rhodium(III)-catalyzed C–H functionalization of alkenyl azoles with diazoketones.[a,b]





[a] Reaction conditions: **1** (0.50 mmol), **4** (1.5 equiv), 0.1 M, 16 h. [b] Yield of isolated products after chromatography on silica. [c] 60 °C. [d] 80 °C, MeOH as solvent. THF = tetrahydrofuran.

tent substrate in the reaction, giving the pyrazolopyridine **3k** upon reaction with 3-hexyne. Notably, coupling an α-chloroalkenyl pyrazole provided the chloro-substituted pyrazolopyridine **3l** in good yield. To our knowledge, this represents the first example of group IX metal-catalyzed C(sp^2)–H haloalkene annulation,[7] and is of utility because chloro substituents on fused [5,6]-bicyclic nitrogen heterocycle frameworks are present in clinical candidates[8] and serve as versatile handles for further elaboration. Finally, alkenyl 1,2,4-triazoles gave the triazolopyridines **3m–r** with a greater than 90:10 cyclization regioselectivity to provide the depicted triazolo[4,3-*a*]pyridines, as confirmed by X-ray crystallography of **3m**.[9]

We next investigated the reaction of alkenyl azoles with the diazoketones **4** (Table 2). These compounds have emerged in the past several years as competent coupling partners for heterocycle synthesis by rhodium(III)-catalyzed C–H functionalization.[10] Unlike for alkyne coupling, the reaction of alkenyl azoles with diazoketones is redox-neutral and requires no stoichiometric oxidant. For C-alkenyl imidazoles, simple heating at 40 °C in THF was effective (see Table S2 for optimization). The reaction of ethyl diazoacetoacetate (**4a**) with alkenyl imidazoles gave the imidazopyridines **3s–v** with ester substituents. A substrate with a methyl substituent on the imidazole ring underwent annulation with high selectivity to give the methyl-substituted imidazopyridine **3w**. It was also possible to vary the identity of the diazoketone substrate. A phenyl ketone coupled efficiently to afford **3x**, and imidazopyridine products containing ketone (**3y**), sulfone (**3z**), and phosphonate (**3aa**) substituents were also synthesized in good to excellent yields.

We next investigated the coupling of alternative alkenyl azoles with diazoketones. Pyrazole and triazole substrates were competent C–H partners, thus giving the products **3ab** and **3ac**, respectively (Table 2). The compound **3ac** was isolated as a single isomer, which was characterized by X-ray crystallography to be distinct from that previously obtained for alkyne coupling (**3m–r**; Table 1).[11]

In addition to the diazoketones substituted with an electron-withdrawing group, when CsOAc was employed as a stoichiometric additive, the phenyl-substituted diazoketone **4f** also coupled to give the products **3ad** and **3ae** (Figure 2a). It can be challenging to develop reactions in which both acceptor/acceptor and donor/acceptor diazo compounds react.[12] To the best of our knowledge, this report represents the first example of rhodium(III)-catalyzed C–H addition into both classes of diazo compounds. Moreover, it is significant that the phenyl diazoketone exclusively provided **3ae**, while the regioisomeric **3c** preferentially formed in the alkyne coupling, thus demonstrating the complementary nature of these approaches (Figure 2b).

It is noteworthy that divergent isomer formation with alkyne and diazoketone coupling partners was also observed for the alkenyl triazole substrates. Reaction with alkynes gave the triazolo[4,3-*a*]pyridines **3m–r** (Table 1), while the reaction with a diazoketone yielded the triazolo[1,5-*a*]pyridine **3ac** (Table 2). The different product outcome can be understood by the disparate mechanisms for product formation (Scheme 1). Alkyne coupling begins with the concerted

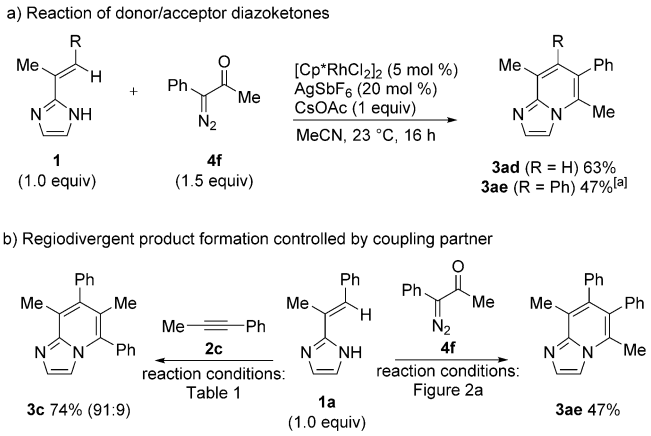
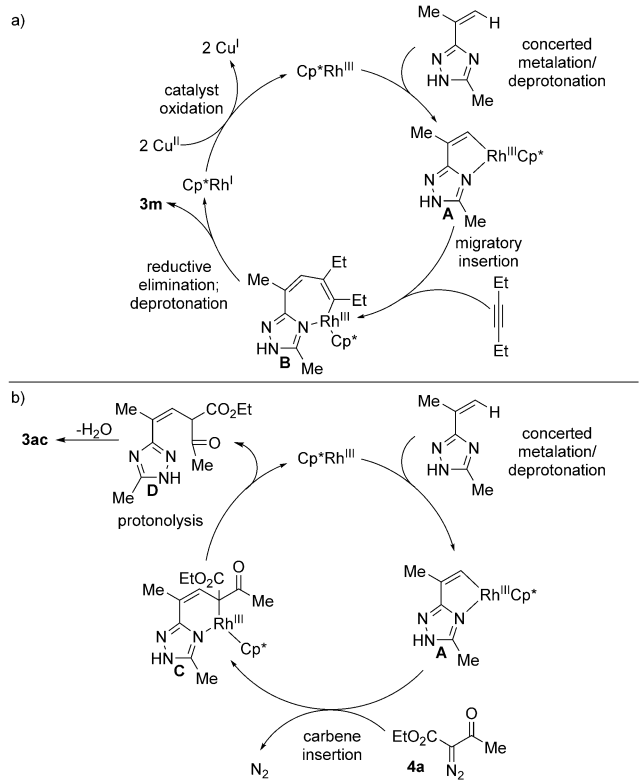


Figure 2. Reaction of donor/acceptor diazoketone allowing divergent product formation. [a] After 16 h, added AcOH (5 mL) and stirred at 100 °C for 24 h.



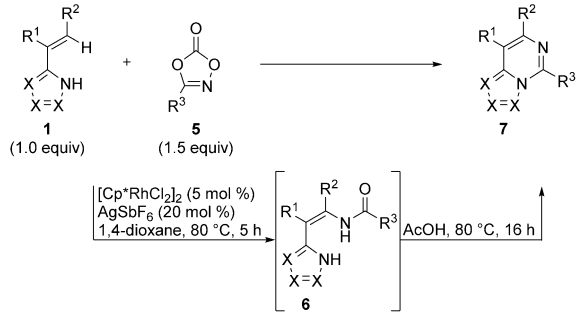
Scheme 1. a) Mechanism of rhodium(III)-catalyzed coupling of alkenyl azoles with alkynes. b) Mechanism of rhodium(III)-catalyzed coupling of alkenyl azoles with diazoketones.

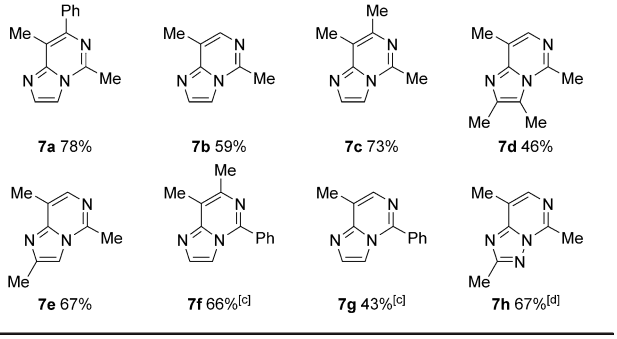
metalation/deprotonation of alkenyl triazole to form the rhodacycle **A** (Scheme 1 a).[13] Migratory insertion of 3-hexyne gives the intermediate **B**, and reductive elimination yields **3 m**. Oxidation of rhodium(I) then regenerates the rhodium(III) catalyst. The isomer formed is determined by selective rhodium coordination at N4 of the 1,2,4-triazole substrate, presumably because the electron density is greatest at this site. Reductive elimination then gives the triazolo[4,3-*a*]pyridine.

In contrast, reaction of a diazoketone with **A** results in loss of nitrogen to give the intermediate **C** (Scheme 1 b). Protonolysis releases the intermediate **D** and regenerates the catalyst. Cyclodehydration of **D** then provides the triazolopyridine **3 ac**. The high regioselectivity for cyclization of **D** likely occurs to avoid unfavorable steric interactions between the triazole methyl group and the methyl ketone.

In addition to azolopyridines, we sought to develop a method for the synthesis of azolopyrimidines, which contain an additional nitrogen atom within the six-membered ring. We investigated the reaction of alkenyl azoles with the dioxazolones **5** (Table 3), which have previously been

Table 3: Rhodium(III)-catalyzed C–H functionalization of alkenyl azoles with dioxazolones.[a,b]



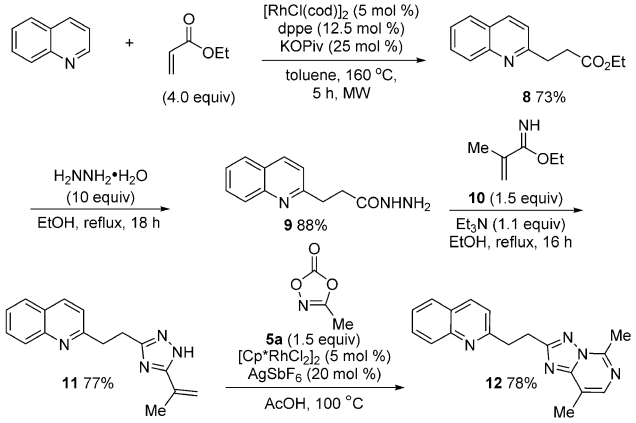


[a] Reaction conditions: **1** (0.50 mmol), **5** (1.5 equiv), 0.1 M, 16 h. [b] Yield of isolated products after chromatography on silica. [c] Second step at 100 °C. [d] Addition and cyclization performed at 80 °C with AcOH as solvent.

employed in rhodium(III)-catalyzed C–H amidation,[14] and found that heating at 80 °C in 1,4-dioxane for five hours was optimal for the synthesis of the enamides **6**. Treatment with acetic acid facilitated cyclization of the enamides to the desired azolopyrimidines **7**. Reaction of alkenyl imidazoles with a methyl-substituted dioxazolone gave the imidazopyrimidines **7 a**–**d** in moderate to high yields. Annulation of a substrate with a methyl group on the imidazole ring afforded the imidazopyrimidine **7 e** with complete selectivity for the methyl group at the 2-position. Reactions with a phenyl-substituted dioxazolone provided products **7 f** and **7 g**. For these entries, a higher temperature was necessary in the second step, as the intermediate enamide cyclizes less efficiently. Finally, the alkenyl 1,2,4-triazole substrate coupled to afford the triazolopyrimidine **7 h**, but required that both the C–H bond addition and cyclization be performed in acetic

acid. This one-step protocol was successful for other substrate pairings, but was lower yielding for the imidazopyrimidines. Selective formation of **7h** occurs during the cyclization step, likely because of minimization of unfavorable steric interactions in analogy to the synthesis of triazolopyridines from diazoketones (Scheme 1b).

The utility of the developed methodology was demonstrated by the modular and iterative application of C–H functionalization methods for the rapid synthesis of **12**, a potential drug candidate for central nervous system (CNS) disorders (Scheme 2).[15] An initial C–H alkylation of quinoline by rhodium(I) catalysis[16] provided **8**, which upon reaction with hydrazine gave the hydrazide **9** in high yield. Condensation of **9** with the imidate **10** afforded the alkenyl-substituted triazole **11**. Final rhodium(III)-catalyzed annulation with the dioxazolone **5a** provided the target compound **12** in 78% yield. By the application of two rhodium-catalyzed C–H functionalization steps, this target could be synthesized in only four steps and in a good overall yield.



Scheme 2. Synthesis of potential drug candidate **12** utilizing developed methodology.

In summary, we have developed novel methods for the synthesis of fused [5,6]-bicyclic heterocycles with a ring-junction nitrogen atom by rhodium(III)-catalyzed C–H functionalization of C-alkenyl azoles. The three different classes of coupling partners that were employed allow the construction of diverse heterocycles of biological relevance. Moreover, the applicability to drug discovery was illustrated by modular and iterative application of C–H functionalization methods for the preparation of a patented compound with CNS activity.

Acknowledgements

This work was supported by the NIH (R35GM122473). We gratefully acknowledge Dr. Brandon Mercado (Yale University) for solving the crystal structures of **3m** and **3ac**. KSH thanks the Villum Foundation for post-doctoral funding (VKR023371).

Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H activation · cyclization · homogeneous catalysis · nitrogen heterocycles · rhodium

How to cite: *Angew. Chem. Int. Ed.* **2017**, *56*, 9183–9187
Angew. Chem. **2017**, *129*, 9311–9315

[1] Typing the names of these drugs and drug candidates into PubChem provides the compound structure, bioactivity, full list of literature, and access to ongoing clinical trials, applications, and usage.
[2] For relevant reviews, see: a) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212; b) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651; c) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; *Angew. Chem.* **2012**, *124*, 9092; d) T. Mesganaw, J. A. Ellman, *Org. Process Res. Dev.* **2014**, *18*, 1097; e) M. Gulías, J. L. Mascareñas, *Angew. Chem. Int. Ed.* **2016**, *55*, 11000; *Angew. Chem.* **2016**, *128*, 11164.
[3] a) J.-R. Huang, Q.-R. Zhang, C.-H. Qu, X.-H. Sun, L. Dong, Y.-C. Chen, *Org. Lett.* **2013**, *15*, 1878; b) L. Dong, J.-R. Huang, C.-H. Qu, Q.-R. Zhang, W. Zhang, B. Han, C. Peng, *Org. Biomol. Chem.* **2013**, *11*, 6142; c) For imidazo[1,2-a]pyridinium salts, see: R. Thenarukandiyil, H. Thrikkykkal, J. Choudhury, *Organometallics* **2016**, *35*, 3007.
[4] Methods have been developed for the direct C–H arylation of pre-assembled azolopyridines and azopyrimidines. For reviews that provide leading references, see: a) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173; b) R. Rossi, M. Lessi, C. Manzini, G. Marianetti, F. Bellina, *Synthesis* **2016**, 3821.
[5] a) N. Umeda, H. Tsurugi, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2008**, *47*, 4019; *Angew. Chem.* **2008**, *120*, 4083; b) K. Morimoto, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 2068; c) X. Li, M. Zhao, *J. Org. Chem.* **2011**, *76*, 8530; d) W. B. Ma, K. Graczyk, L. Ackermann, *Org. Lett.* **2012**, *14*, 6318; e) N. Kavitha, G. Sukumar, V. P. Kumar, P. S. Mainkar, S. Chandrasekhar, *Tetrahedron Lett.* **2013**, *54*, 4198; r) R. Wang, J. R. Falck, *J. Organomet. Chem.* **2014**, *759*, 33; g) L. Zheng, R. Hua, *J. Org. Chem.* **2014**, *79*, 3930; h) A. G. Algarra, W. B. Cross, D. L. Davies, Q. Khamker, S. A. Macgregor, C. L. McMullin, K. Singh, *J. Org. Chem.* **2014**, *79*, 1954.
[6] For the synthesis of pyridinylamines by C–H functionalization and ring fragmentation of alkenyl oxadiazolones, see: X. Yu, K. Chen, Q. Wang, S. Guo, S. Zha, J. Zhu, *Angew. Chem. Int. Ed.* **2017**, *56*, 5222; *Angew. Chem.* **2017**, *129*, 5306.
[7] For C–H halogenation of an alkenyl bromide, see: N. Kuhl, N. Schröder, F. Glorius, *Org. Lett.* **2013**, *15*, 3860.
[8] See PubChem Compound Identifier numbers 54897 (alpidem) and 68234908.
[9] CCDC 1509748 (**3m**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. See SI for additional details.
[10] Selected examples: a) W.-W. Chan, S.-F. Lo, Z. Zhou, W.-Y. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 13565; b) Z. Shi, D. C. Koester, M. Boultadakis-Arapnis, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 12204; c) L. Shi, K. Yu, B. Wang, *Chem. Commun.* **2015**, *51*, 17277; d) Y. Wu, P. Sun, K. Zhang, T. Yang, H. Yao, A. Lin, *J. Org. Chem.* **2016**, *81*, 2166; e) X. G. Li, M. Sun, Q. Jin, K. Liu, P. N. Liu, *J. Org. Chem.* **2016**, *81*, 3901; f) X. Chen, X. Hu, S. Bai, Y. Deng, H. Jiang, W. Zeng, *Org. Lett.* **2016**, *18*, 192.
[11] CCDC 1509749 (**3ac**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[12] T. K. Hyster, K. E. Ruhl, T. Rovis, *J. Am. Chem. Soc.* **2013**, *135*, 5364.
[13] a) L. Li, W. W. Brennessel, W. D. Jones, *J. Am. Chem. Soc.* **2008**, *130*, 12414; b) A. P. Walsh, W. D. Jones, *Organometallics* **2015**, *34*, 3400.
[14] For a review, see: a) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, https://doi.org/10.1021/acs.chemrev.6b00644; For selected examples: b) Y. Park, K. T. Park, J. G. Kim, S. Chang, *J. Am. Chem. Soc.* **2015**, *137*, 4534; c) H. Wang, G. D. Tang, X. W. Li, *Angew. Chem. Int. Ed.* **2015**, *54*, 13049; *Angew. Chem.* **2015**, *127*, 13241; d) J. Wang, S. Zha, K. Chen, F. Zhang, C. Song, J. Zhu, *Org. Lett.* **2016**, *18*, 2062; e) Q. Wang, F. Wang, X. Yang, X. Zhou, X. Li, *Org. Lett.* **2016**, *18*, 6144.
[15] J. E. Campbell, M. C. Hewitt, P. Jones, L. Xie, *PCT Int. Appl.* **2011**, 150156.
[16] G. Tran, K. D. Hesp, V. Mascitti, J. E. Ellman, *Angew. Chem. Int. Ed.* **2017**, *56*, 5899; *Angew. Chem.* **2017**, *129*, 5993.

Manuscript received: April 17, 2017
Accepted manuscript online: June 6, 2017
Version of record online: July 5, 2017

