Organic LETTERS

Letter

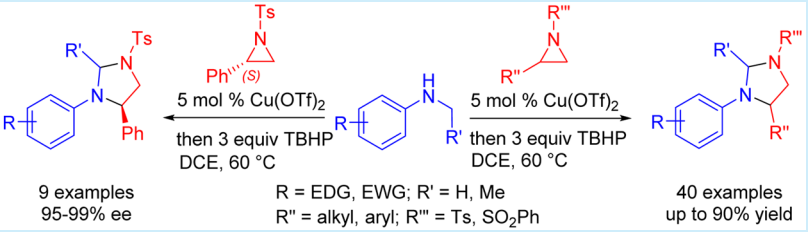
pubs.acs.org/OrgLett

Stereospecific Copper-Catalyzed Domino Ring Opening and sp^3 C–H Functionalization of Activated Aziridines with *N*-Alkylanilines

Mani Sengoden, Abhisikta Bhowmick, and Tharmalingam Punniyamurthy*

Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781039, India

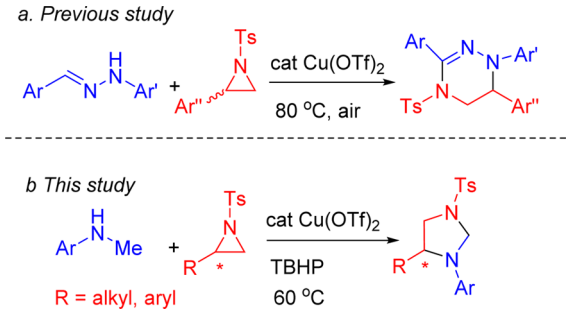
Supporting Information



ABSTRACT: Copper efficiently catalyzed nucleophilic ring opening, sp^3 C–H functionalization, and C–N bond formation in the presence of *tert*-butyl hydroperoxide to afford functionalized imidazolidines starting from *N*-sulfonylaziridines and *N*-alkylanilines. The products were obtained in high optical purities (95 → 99% ee) with excellent functional group tolerance.

Recent advances in transition-metal catalysis have led to the development of effective methods for regioselective carbon–carbon and carbon–heteroatom bond formation.[1,2] Among these, the construction of C–N bonds has attracted considerable attention since nitrogen-containing heterocycles have broad applications in the biological and medicinal sciences.[1a,b,3] Aziridines are versatile building blocks in organic synthesis, and several excellent examples have been reported involving nucleophilic ring opening.[4,5] Recently, Wang and co-workers described a copper(II)-catalyzed domino ring opening and sp^2-C–H functionalization of racemic aziridines to produce tetrahydrotriazines (Scheme 1a).[6] This tandem strategy provides an effective synthetic tool for the construction of two C–N bonds in one-pot without isolating the intermediates, which greatly enhances the synthetic efficiency.[7] As a continuation of our studies on domino reaction of aziridines,[5e] we report an efficient stereospecific copper(II)-catalyzed nucleophilic ring opening (S_N2) and sp^3 C–H functionalization of *N*-sulfonylaziridines with *N*-alkylanilines using *tert*-butyl hydroperoxide (TBHP)[8] to produce imidazolidines that are important in synthetic and medicinal sciences (Scheme 1b).[9−12] This protocol provides a potential route for the selective construction of the target five-membered heterocycles with excellent substrate scope and optical purities.

Scheme 1. Domino Reaction of Aziridines with Aniline Derivatives



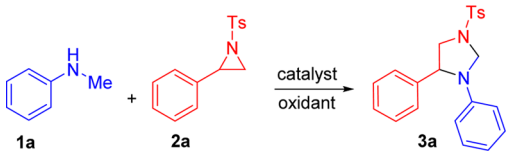
First, the reaction conditions were optimized using *N*-methylaniline **1a** and 2-phenyl-1-tosylaziridine **2a** as the model substrates and varying copper sources, oxidants, and solvents (Table 1). The reaction produced imidazolidine **3a** in 53% conversion when substrates **1a** and **2a** were stirred at 60 °C for 6 h using 5 mol % of $Cu(OTf)_2$ and 3.0 equiv of TBHP in toluene. Between the four Cu sources screened, $Cu(OTf)_2$ $Cu(OAc)_2$, $CuCl_2$, and $Cu(NO_3)_2{\cdot}3H_2O$, the $Cu(OTf)_2$ afforded the highest conversion (entries 2–4). Subsequent screening of the solvents revealed that the reaction went to completion in 1 h with 100% conversion using 1,2-dichloroethane, whereas THF, DMSO, and $CHCl_3$ furnished **3a** in 66–85% conversion (entries 5–8). When the quantity of TBHP was decreased to 2.5 equiv, a slightly longer reaction time (5 h) was required to produce **3a** in 89% conversion (entry 9). When the reaction was conducted using O_2 and urea·H_2O_2 as the oxidants, **3a** was formed in 8–9% conversions (entries 11 and 12). A control experiment confirmed that the formation of **3a** was not observed in the absence of $Cu(OTf)_2$.

Using the optimized conditions, the substrate scope was studied for the reaction of substituted anilines **1b–s** with aziridine **2a** as a standard substrate (Scheme 2). *N*-Methylanilines **1b–e** and **1g–m** with 2-chloro, 3-cyano, 3-methoxy, 3-methyl, 4-cyano, 4-isopropyl, 4-methyl, 4-nitro, 4-methylthio, 4-(trimethylsilyl)ethynyl, and 4-trifluoromethoxy substituents in the aryl ring underwent reaction to furnish imidazolidines **3b–e**

Received: November 19, 2016

DOI: 10.1021/acs.orglett.6b03458
Org. Lett. XXXX, XXX, XXX–XXX

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	catalyst	oxidant	solvent	time (h)	conv of 3a[b] (%)
1	$Cu(OTf)_2$	TBHP	toluene	6	53
2	$Cu(OAc)_2$	TBHP	toluene	6	18
3	$CuCl_2$	TBHP	toluene	6	23
4	$Cu(NO_3)_2 \cdot 3H_2O$	TBHP	toluene	6	39
5	$Cu(OTf)_2$	TBHP	$(CH_2Cl)_2$	1	100
6	$Cu(OTf)_2$	TBHP	THF	1	66
7	$Cu(OTf)_2$	TBHP	DMSO	1	72
8	$Cu(OTf)_2$	TBHP	$CHCl_3$	1	85
9	$Cu(OTf)_2$	TBHP	$(CH_2Cl)_2$	5	89[c]
10	$Cu(OTf)_2$	O_2	$(CH_2Cl)_2$	1	9
11	$Cu(OTf)_2$	urea•H_2O_2	$(CH_2Cl)_2$	1	8
12	-	TBHP	$(CH_2Cl)_2$	1	nr

[a]Reaction conditions: **1a** (0.55 mmol), **2a** (0.5 mmol), catalyst (5 mol %), solvent (1 mL), 60 °C for 1 h; TBHP (1.5 mmol), 60 °C. [b]Determined by 400 MHz ^{1}H NMR spectroscopy. [c]TBHP (1.25 mmol) used. n.d. = not detected. n.r. = no reaction.

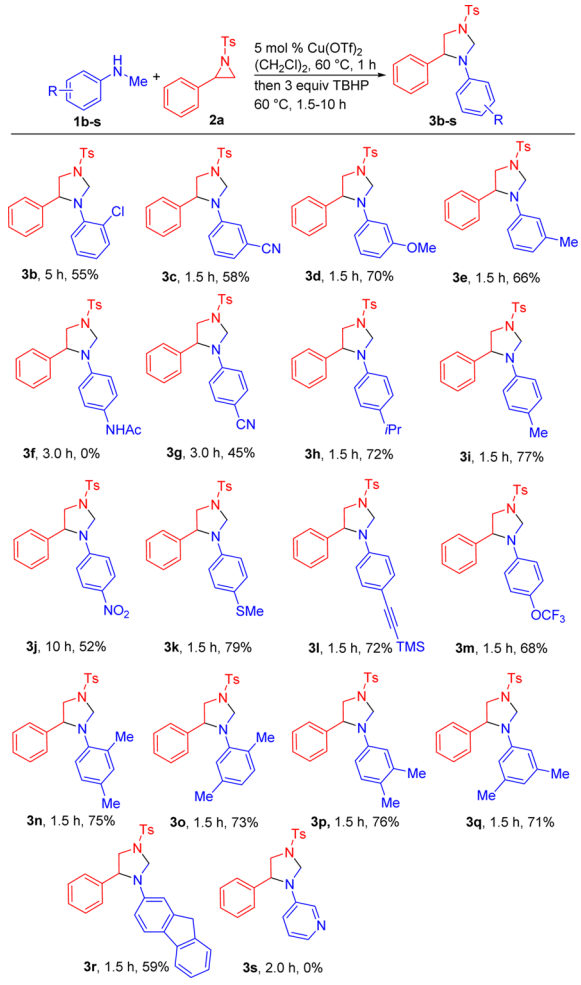
and **3g**−**m** in 45−79% yields. The reaction of *N*-methylanilines **1n**−**q** bearing 2,4-dimethyl, 2,5-dimethyl, 3,4-dimethyl, and 3,5-dimethyl substituents afforded imidazolidines **3n**−**q** in 71−76% yields. Further, *N*-(methylamino)fluorene **1r** underwent reaction to give imidazolidine **3r** in good yield. In contrast, *N*-methylaniline **1f** bearing a 4-amido group in the aryl ring led to the nucleophilic ring opening of **2a**; however, the subsequent cyclization had not occurred to yield **3f**. In addition, *N*-methylpyridin-3-amine **1s** showed no reaction with **2a** to yield **3s**. These results may be due to the chelation of the 4-amido **1f** and pyridine nitrogen **1s** functionalities to $Cu(OTf)_2$.

Next, the reaction of anilines with different *N*-alkyl substituents was studied (Scheme 3). *N*-Ethylaniline underwent reaction to give imidazolidine **3t** in moderate yield. In contrast, *N*-benzyl- and *N*-isopropylanilines failed to produce the desired products **3u**−**v**, which may be due to the steric hindrance of the alkyl substituents. However, tetrahydroisoquinoline **1w** underwent reaction to provide the tricyclic imidazolidine **3w** in 90% yield. The relative configuration of **3t** and **3w** was determined using 2D NOESY (see the Supporting Information).

The protocol was further extended to the reaction of a series of substituted *N*-tosylaziridines **2b**−**r** with *N*-methylaniline **1a** as a representative example (Scheme 4). Aziridines **2b**−**k** containing 2-chloro, 2-methyl, 3-bromo, 3-chloro, 4-acetoxy, 4-CH_2Cl, 4-bromo, 4-chloro, 4-fluoro, and 4-methyl substituents in the aryl ring reacted to furnish the corresponding functionalized imidazolidines **3x**−**ag** in 69−89% yields. The reaction of 2-arylaziridines bearing 2,4-dimethyl (**2l**) and 2,4,6-trimethyl (**2m**) substituents produced imidazolidines **3ah** and **3ai** in 63% and 80% yield, respectively. Similar results were observed for 2-naphthyl- (**2n**), 2-*n*-hexyl- (**2o**), 2-*n*-octyl- (**2p**), and 2-*n*-decyl-substituted (**2q**) aziridines, affording **3aj**−**am** in 61−81% yields. In addition, *N*-(phenylsulfonyl)-2-arylaziridine (**2p**) underwent reaction to give the desired imidazolidine **3an** in 82% yield.

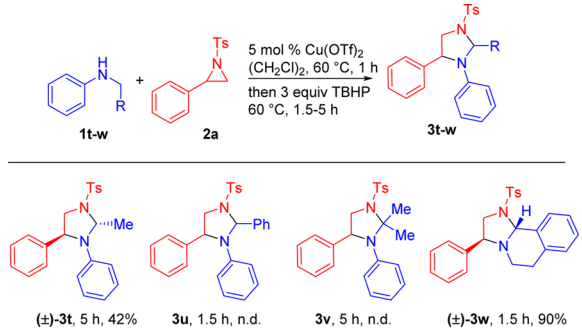
Finally, the enantiospecific synthesis of imidazolidines was investigated with a series of *N*-methylanilines using optically

Scheme 2. Reaction of *N*-Methylanilines with Aziridine 2a[a,b]



[a]Reaction condition: **1b**−**s** (0.55 mmol), **2a** (0.5 mmol), $Cu(OTf)_2$ (5 mol %), $(CH_2Cl)_2$ (1 mL), 60 °C, 1 h; TBHP (1.5 mmol). [b]Isolated yield.

Scheme 3. Reaction of *N*-Alkylanilines with Aziridine 2a[a,b]

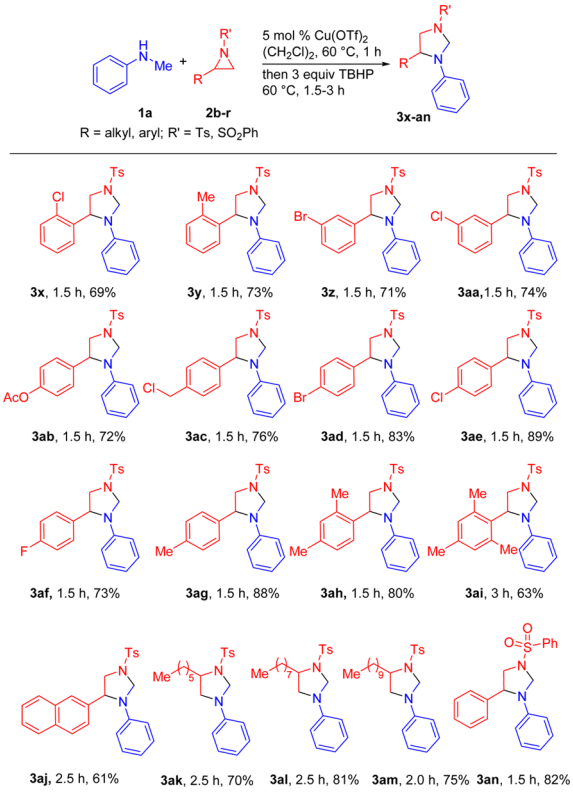


[a]Reaction conditions: **1t**−**w** (0.55 mmol), **2a** (0.5 mmol), $Cu(OTf)_2$ (5 mol %), $(CH_2Cl)_2$ (1 mL), 60 °C, 1 h; TBHP (1.5 mmol). [b]Isolated yield.

active aziridine **2a′** as a standard substrate (Scheme 5). This reaction took place to afford the corresponding functionalized imidazolidines with excellent optical purities (>95% ee). For example, *N*-methylaniline underwent reaction to give imidazolidine **3a′** in 97% ee, whereas *N*-methylanilines containing 3-methyl, 4-methyl, 4-isopropyl, 2,4-dimethyl, 2,5-dimethyl, 3,4-

DOI: 10.1021/acs.orglett.6b03458
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Reaction of 1a with Substituted Aziridines[a,b]

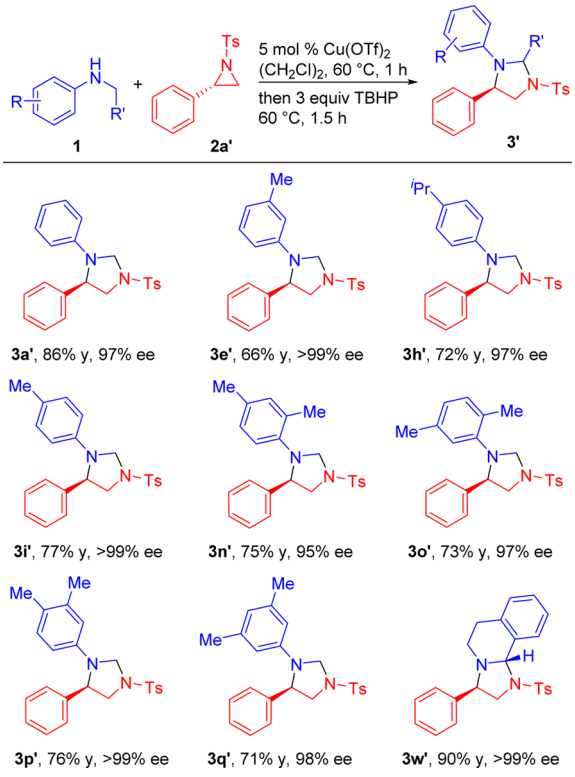


[a]Reaction condition: **1a** (0.55 mmol), **2b−r** (0.5 mmol), $Cu(OTf)_2$ (5 mol %), $(CH_2Cl)_2$ (1 mL), 60 °C, 1 h; TBHP (1.5 mmol). [b]Isolated yield.

dimethyl and 3,5-dimethyl substituents in the aryl ring produced the corresponding imidazolidine derivatives **3e′**, **3h′**,**i′**, and **3n′**−**q′** in 95−99% ee. A similar result was observed with tetrahydroisoquinoline, affording **3w′** in 99% ee, whose structure and absolute configuration were determined using single-crystal X-ray analysis (see the Supporting Information). These results suggest that the protocol can be utilized for the enantiospecific synthesis of imidazolidines with excellent optical purity.

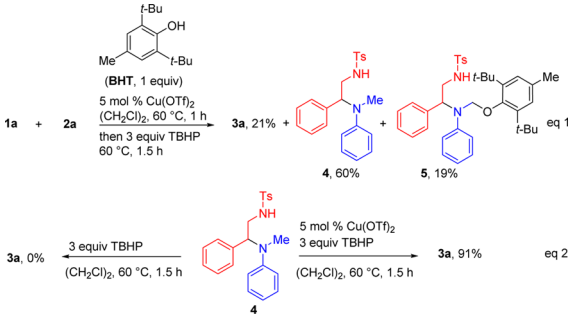
To gain insight into the catalytic cycle, the reaction of **1a** was performed with **2a** in the presence of 1 equiv of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical scavenger (Scheme 6, eq 1). ^{1}H NMR and ESI-MS analyses of the reaction mixture revealed the formation of BHT adduct **5** along with the acyclic 1,2-diamine derivative **4** and imidazolidine **3a** (see the Supporting Information).[13] Next, the cyclization of **4** was investigated using $Cu(OTf)_2$ and TBHP (Scheme 6, eq 2). The reaction occurred to produce **3a** in 91% yield. However, in the absence of $Cu(OTf)_2$, **4** showed no reaction (Scheme 6, eq 2). These results suggest that the *N*-methyl C−H bond selectively undergoes homolysis compared to the benzylic C−H bond. This effect may be due to the steric hindrance of the benzylic C−H bond toward the bulky BHT radical. Thus, coordination of $Cu(OTf)_2$ with the nitrogen lone pair of aziridine and its subsequent S_N2 reaction with *N*-methylaniline can give ***a*** (Scheme 7).[5e] Single-electron transfer (SET) reduction of $Cu(OTf)_2$ using the nitrogen lone pair of ***a*** may lead to the formation of an intermediate ***b***.[2e] Homolysis of the *N*-methyl C−H bond using *tert*-butoxy radical can generate imine derivative ***c***, which may lead to cyclization to furnish the target heterocycles. Oxidation of $Cu(OTf)_2^-$ using TBHP may regenerate $Cu(OTf)_2$ to complete the catalytic cycle.

Scheme 5. Reaction of *N*-Alkylanilines with Chiral Aziridine 2a′[a−c]

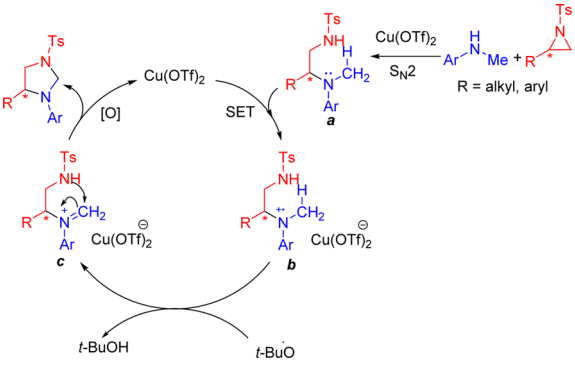


[a]Reaction condition: **1** (0.55 mmol), **2a−** (0.5 mmol), $Cu(OTf)_2$ (5 mol %), $(CH_2Cl)_2$ (1 mL), 60 °C, 1 h; TBHP (1.5 mmol). [b]Isolated yield. [c]Determined by HPLC using Chiralcel OD with 2-propanol and hexane as eluent (1:9).

Scheme 6. Control Experiments



Scheme 7. Proposed Catalytic Cycle



DOI: 10.1021/acs.orglett.6b03458
Org. Lett. XXXX, XXX, XXX−XXX

The proposed catalytic cycle also explains the requirement of excess TBHP to achieve high yields of the products.

In summary, a copper-catalyzed domino reaction of *N*-alkylanilines with aziridines is presented for the construction of 1,3-imidazolidines in the presence of TBHP via a sequence of selective nucleophilic ring opening (S_N2), C(sp^3)−H functionalization, and C−N bond formation. The regio- and stereospecificities, shorter reaction time, high yields, and functional group tolerance are important practical advantages of this strategy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03458.

Experimental procedures, characterization data, HPLC chromatograms, ^{1}H NMR and HRMS of the reaction mixture of **3a**, **4**, and **5**, and NMR spectra of the products (PDF)

X-ray data for compound **3w′** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tpunni@iitg.ernet.in.

ORCID

Tharmalingam Punniyamurthy: 0000-0003-4696-8896

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Science and Engineering Research Board (EMR-2015-43) and the Council of Scientific and Industrial Research (02(0255)/16/EMR-II) for financial support. M.S. thanks the University Grants Commission. A.B. thanks the Council of Scientific and Industrial Research for Research Fellowships. We are grateful to the Central Instrumentation Facility, Indian Institute of Technology Guwahati, for NMR, single-crystal X-ray, and mass facilities.

■ REFERENCES

(1) For some reviews, see: (a) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657. (b) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (c) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (d) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (e) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (f) Louillat, M.-L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901. (g) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053.

(2) For some examples, see: (a) Murahashi, S.-I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005. (b) Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, 5024. (c) Kumaraswamy, G.; Murthy, A. N.; Pitchaiah, A. *J. Org. Chem.* **2010**, *75*, 3916. (d) Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc.* **2012**, *134*, 5317. (e) Xia, Q.; Chen, W. *J. Org. Chem.* **2012**, *77*, 9366. (f) Zhang, J.; Tiwari, B.; Xing, C.; Chen, X.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 3649. (g) Ratnikov, M. O.; Doyle, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 1549. (h) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062. (i) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110. (j) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (k) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun.* **2014**, *50*, 29. (l) Zhao, D.; Lied, F.; Glorius, F. *Chem. Sci.* **2014**, *5*, 2869. (m) Wang, L.; Priebbenow, D. L.; Dong, W.; Bolm, C. *Org. Lett.* **2014**, *16*, 2661. (n) Spangler, J. E.; Kobayashi, Y.; Verma, P.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 11876.

(3) For examples, see: Espino, C. G.; Du Bois, J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005.

(4) For recent reviews of the reaction of aziridines, see: (a) Cardoso, A. L.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2012**, 6479. (b) Callebaut, G.; Meiresonne, T.; De Kimpe, N.; Mangelinckx, S. *Chem. Rev.* **2014**, *114*, 7954.

(5) For some examples, see: (a) Butler, C. D.; Inman, A. G.; Alper, H. *J. Org. Chem.* **2000**, *65*, 5887. (b) Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 11836. (c) Munegumi, T.; Azumaya, I.; Kato, T.; Masu, H.; Saito, S. *Org. Lett.* **2006**, *8*, 379. (d) Wu, J.-Y.; Luo, Z.-B.; Dai, L.-X.; Hou, X.-L. *J. Org. Chem.* **2008**, *73*, 9137. (e) Sengoden, M.; Punniyamurthy, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 572. (f) Craig, R. A.; O'Connor, N. R.; Goldberg, A. F. G.; Stoltz, B. M. *Chem. - Eur. J.* **2014**, *20*, 4806. (g) Schneider, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2082. (h) Ghorai, M.; Sahoo, A. K.; Kumar, S. *Org. Lett.* **2011**, *13*, 5972. (i) Takeda, Y.; Kuroda, A.; Sameera, W. M. C.; Morokuma, K.; Minakata, S. *Chem. Sci.* **2016**, *7*, 6141.

(6) Hong, D.; Lin, X.; Zhu, Y.; Lei, M.; Wang, Y. *Org. Lett.* **2009**, *11*, 5678.

(7) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(8) Caution: the concentration of peroxide-containing mixtures is an explosive hazard. Take appropriate safety measures including, but not limited to, the use of a blast shield and other personal protective equipment. Decomposition of any remaining peroxides prior to concentration is a best practice.

(9) For imidazolidines ligands and catalysts, see: (a) Citadelle, C. A.; Nouy, E. L.; Bisaro, F.; Slawin, A. M. Z.; Cazin, C. S. J. *Dalton Trans.* **2010**, *39*, 4489. (b) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 4260. (c) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485.

(10) For biological properties, see: (a) Karunker, I.; Morou, E.; Nikou, D.; Nauen, R.; Sertchook, R.; Stevenson, B. J.; Paine, M. J. I.; Morin, S.; Vontas, J. *Insect Biochem. Mol. Biol.* **2009**, *39*, 697. (b) Akamatsu, M. *J. Agric. Food Chem.* **2011**, *59*, 2909. (c) Moussa, I. A.; Banister, S. D.; Manoli, M.; Doddareddy, M. R.; Cui, J.; Mach, R. H.; Kassiou, M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5493. (d) Xu, R.; Xia, R.; Luo, M.; Xu, X.; Cheng, J.; Shao, X.; Li, Z. *J. Agric. Food Chem.* **2014**, *62*, 381.

(11) For a classical approach, see: Katritzky, A. R.; Suzuki, K.; He, H.-Y. *J. Org. Chem.* **2002**, *67*, 3109.

(12) For modern methods, see: (a) Xie, H.; Zhu, J.; Chen, Z.; Li, S.; Wu, Y. *J. Org. Chem.* **2010**, *75*, 7468. (b) Saima, Y.; Khamarui, S.; Gayen, K. S.; Pandit, P.; Maiti, D. K. *Chem. Commun.* **2012**, *48*, 6601. (c) Li, Q.-H.; Wei, L.; Chen, X.; Wang, C.-J. *Chem. Commun.* **2013**, *49*, 6277. (d) Swain, S. P.; Shih, Y.-C.; Tsay, S.-C.; Jacob, J.; Lin, C.-C.; Hwang, K. C.; Horng, J.-C.; Hwu, J. R. *Angew. Chem., Int. Ed.* **2015**, *54*, 9926. (e) Izquierdo, C.; Esteban, F.; Ruano, J. L. G.; Fraile, A.; Aleman, J. *Org. Lett.* **2016**, *18*, 92. (f) Wang, Y.-M.; Zhang, H.-H.; Li, C.; Fan, T.; Shi, F. *Chem. Commun.* **2016**, *52*, 1804. (g) van Benthem, R. A. T. M.; Hiemstra, H.; Longarela, G. R.; Speckamp, W. N. *Tetrahedron Lett.* **1994**, *35*, 9281. (h) Nenajdenko, V. G.; Muzalevskiy, V. M.; Shastin, A. V.; Balenkova, E. S.; Kondrashov, E. V.; Ushakov, I. A.; Rulev, A. Y. *J. Org. Chem.* **2010**, *75*, 5679. (i) Xuan, J.; Cheng, Y.; An, J.; Lu, L.-Q.; Zhang, X.-X.; Xiao, W.-J. *Chem. Commun.* **2011**, *47*, 8337. (j) Elliott, L. D.; Wrigglesworth, J. W.; Cox, B.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Org. Lett.* **2011**, *13*, 728.

(13) Wagner, A.; Ofial, A. R. *J. Org. Chem.* **2015**, *80*, 2848.

DOI: 10.1021/acs.orglett.6b03458
Org. Lett. XXXX, XXX, XXX−XXX