JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Rh_2(II)-Catalyzed Ring Expansion of Cyclobutanol-Substituted Aryl Azides To Access Medium-Sized *N*-Heterocycles

Wrickban Mazumdar,[†] Navendu Jana,[†] Bryant T. Thurman,[†] Donald J. Wink,[†] and Tom G. Driver*[,†,‡]

[†]Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061, United States
[‡]Institute of Next Generation Matter Transformation, College of Chemical Engineering, Huaqiao University, 668 Jimei Boulevard, Xiamen, Fujian 361021, People's Republic of China

Supporting Information

ABSTRACT: A new reactivity pattern of Rh_2(II)-*N*-arylnitrenes was discovered that facilitates the synthesis of medium-sized *N*-heterocycles from *ortho*-cyclobutanol-substituted aryl azides. The key ring-expansion step of the catalytic cycle is both chemoselective and stereospecific. Our mechanistic experiments implicate the formation of a rhodium *N*-arylnitrene catalytic intermediate and reveal that sp^3 C−H bond amination of this electrophilic species is competitive with the ring-expansion process.

The development of processes that tease new reactivity out of catalytic intermediates continues to spur synthetic chemists toward innovative solutions that access *N*-heterocycles.[1] Constructing these scaffolds using metal divalent catalytic intermediates to trigger domino reactions is rare despite the potential of these reactions to dramatically increase the complexity of the substrates.[2] Azides are emerging as valuable precursors for nitrenes in transition-metal-catalyzed N-atom-transfer reactions, but an electron-withdrawing N-substituent is generally required for the best outcome.[3,4] Our investigations into the reactivity of rhodium *N*-aryl nitrenes have established them as valuable electrophilic catalytic intermediates for the synthesis of complex indoles from readily accessible styryl azides.[5,6] During the course of our studies, we were curious if the electrophilicity of **2** could be harnessed to participate in other bond-forming reactions instead of initiating electrocyclization−migration or C−H bond amination reactions. In particular, we wondered if this electrophilicity could trigger the release of the strain embedded in the *ortho*-substituent of aryl azide **4** to generate an aza-*o*-quinonoid reactive intermediate, such as **6**, which could further rearrange (Scheme 1).[7−9] If successful, this unprecedented ring expansion might access medium-sized heterocycles, which are challenging to construct with existing metal-catalyzed N-atom-transfer reactions.[10] Herein, we report our method development and mechanistic experiments to form these important *N*-heterocycles from aryl azides.

To test our hypothesis, the reactivity of aryl azide **8a** toward commercially available transition metal catalysts was examined (Table 1). The substrates for our study could be constructed in three steps from *N*-phenyl-*tert*-butyl carbamate: the *o*-cyclobutanol group was installed through *o*-lithiation of **7a**;[11] subsequent HCl-mediated Boc-deprotection followed by azidation using *t*-BuONO and Me_3SiN_3 furnished **8a**.[12] In line with our hypothesis, exposure of aryl azide **8a** to a Rh_2(II)-carboxylate catalyst triggered a ring expansion to produce benzazepinone **9a**. The yield of this transformation depended upon the identity of the carboxylate ligand (entries 1−6). While poor conversion was observed with electron-rich rhodium carboxylates (entries 2 and 3), perfluorinated complexes were significantly more active (entries 4 and 5). The highest yield of the benzazepinone was obtained using $Rh_2(esp)_2$ (entry 6).[13] The success of $Rh_2(esp)_2$ is attributed to its tetradentate

Scheme 1. Trigger Ring-Expansion Reactions Using Metal *N*-Aryl Nitrenes

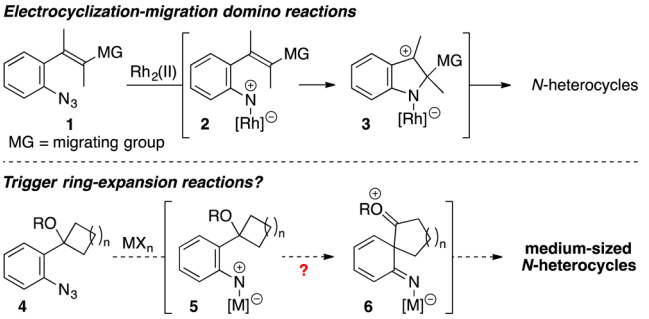
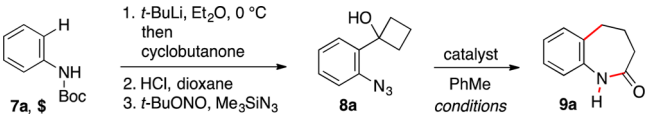


Table 1. Optimization of the Ring Expansion



entry	catalyst	mol%	T (°C)	yield (%)[a]
1	none	n.a.	130	trace
2	$Rh_2(O_2CCH_3)_4$	5	100	24
3	$Rh_2(O_2CC_7H_{15})_4$	5	100	15
4	$Rh_2(O_2CCF_3)_4$	5	100	47
5	$Rh_2(O_2CC_3F_7)_4$	5	100	66
6	$Rh_2(esp)_2$	5	120	71
7	$Rh_2(esp)_2$	1	120	80
8	$RuBr_3 \cdot nH_2O$	1	120	23
9	CoTPP	5	120	trace
10	$[Ir(cod)(OMe)]_2$	n.a.	120	23

[a]Isolated yield after silica gel chromatography.

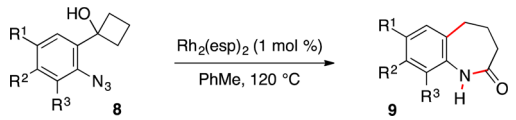
Received: February 23, 2017

DOI: 10.1021/jacs.7b01833
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

ligands, which confer enhanced thermal stability relative to other rhodium carboxylate complexes.[14] The catalyst loading of $Rh_2(esp)_2$ could be lowered to 1 mol % if the reaction temperature was increased to 120 °C (entry 7). Examination of other established N-atom-transfer catalysts or Lewis acids revealed the uniqueness of Rh_2(II)-carboxylates to trigger this transformation: no reaction was observed using iron[15] or copper catalysts,[16] and diminished conversion to benzazepinone **9a** was obtained using $RuBr_3$,[17] CoTPP or [Ir(cod)(OMe)]$_2$ complexes (entries 8–10).[18,19] Other common Lewis acids known to trigger semipinacol rearrangements were found to lead to deleterious results.[20] A solvent screen was performed to determine if the yield or catalyst loading could be further reduced. The use of other chlorinated or ethereal solvents, however, only led to attenuated yields of benzazepinone **9a**.[20]

The scope and limitations of our Rh_2(II)-catalyzed ring-expansion reaction was explored using the optimal conditions (Table 2). While our reaction is currently limited to aryl azides,[21] both electron-donating and electron-withdrawing R^1 and R^2 substituents on the aryl azide were tolerated without attenuating the benzazepinone yield (**9a**–**9e**). In contrast to our previously reported aryl azide methods,[5,6] aryl azide **8k** could be substituted with an additional *ortho*-substituent and still furnish benzazepinone **9k** using the optimal reaction conditions without significant diminishment of the yield.

Table 2. Scope and Limitations of Benzazepinone Formation

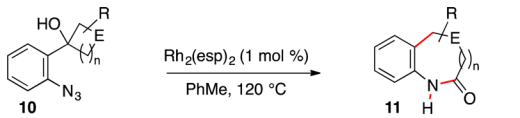


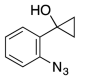
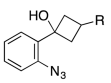
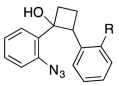
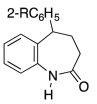
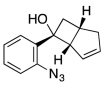
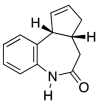
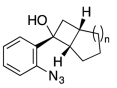
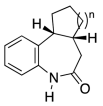
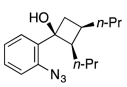
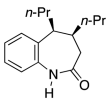
entry		R^1	R^2	R^3	yield (%)[a]
1	**a**	H	H	H	80
2	**b**	OMe	H	H	80
3	**c**	Me	H	H	91[b]
4	**d**	CF_3	H	H	74
5	**e**	OCF_3	H	H	71
6	**f**	H	OMe	H	85
7	**g**	H	Me	H	80
8	**h**	H	F	H	78
9	**i**	H	CF_3	H	86
10	**j**	Me	F	H	80
11	**k**	H	H	OMe	74

[a]Isolated after silica gel chromatography. [b]Cambridge Crystallographic Database number for **9c** is CCDC 1525478.

Next, the identity of the *o*-cycloalkanol substituent of the aryl azide was varied to investigate the scope and selectivity of benzazepinone formation (Table 3). First, aryl azide **10a** established the generality of this phenomenon by revealing that the strain embedded in an *o*-cyclopropanol substituent could be released to access dihydroquinolone **11a** (entry 1). Aryl azide **10b** revealed that our reaction tolerated the presence of an oxygen heteroatom in the strained *ortho*-substituent to access medium-ring *N*-heterocycle **11b**, albeit in a slightly diminished yield (entry 2). The *o*-cyclobutanol substituent could be substituted with an alkyl or aryl substituent to enable access to 4-substituted benzazepinones (entries 3 and 4). The specificity of the [1,2] migration step was investigated with aryl azides **10e**–**10j** (entries 5–10). In contrast to related ring-expansion reactions of substituted cyclobutanols containing N_2 as the leaving group,[22] our reaction proved to be selective: each

Table 3. Investigation of the Scope and Selectivity



entry	#	aryl azide	*N*-heterocycle	yield, %[a]
1[b]	a			80
2	b			51
3 4	c d			R = *t*-Bu, 66 R = Ph, quant
5 6	e f			R = H, 72 R = Br, 66
7	g			60[b]
8 9	h i			n = 1, 73[b] n = 4, 95[b]
10	j			65[b,c]

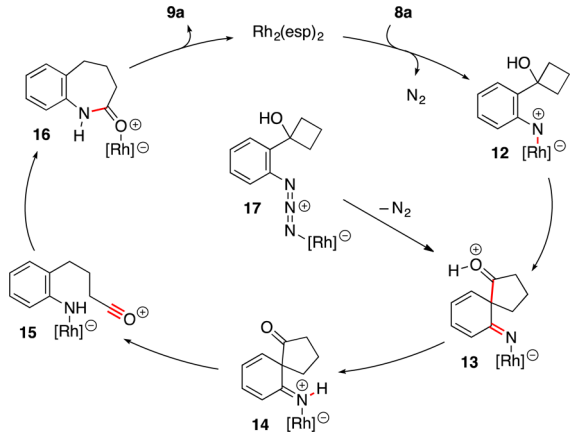
[a]Isolated yield of **11** after silica gel chromatography; only product obtained. [b]d.r. > 95:5. [c]Diastereoselectivity of the product confirmed by X-ray crystallographic analysis. Cambridge Crystallographic Database number for **11j** is CCDC 1525486.

substrate submitted to the reaction conditions produced the medium-ring *N*-heterocycle as a single constitutional isomer. Aryl azides **10e** and **10f** exhibited exclusive migration of the benzyl carbon over the methylene (entries 5 and 6), while only allyl carbon migration was observed with aryl azide **10g** to provide benzazepinone **11g** as the only product (entry 7). Our reaction could even differentiate between the methylene and methine carbons present on the *o*-cyclobutanol substituent: aryl azides **10h** and **10i** produced only the benzazepinone resulting from migration of cycloalkyl fragment (entries 8 and 9). Finally, the stereospecificity of the [1,2] migration step was established with aryl azide **10j** (entry 10). Exposure of the *cis*-substituted **10j** to reaction conditions produced benzazepinone **11j** as a single diastereomer, suggesting that the [1,2] migration is concerted.

The reactivity trends of the *o*-cyclobutanol-substituted aryl azides suggest that the benzazepinone product is formed through the catalytic cycle outlined in Scheme 2. First, the substrate reacts with the Rh_2(II) carboxylate catalyst to form the metal *N*-aryl nitrene **12**.[6,23] Formation of this electrophilic species triggers the selective and stereospecific ring expansion of the *o*-cyclobutanol substituent to produce metallo aza-quinonoid **13**.[9,24] After proton transfer to the metalloimine, aromaticity is re-established by generation of acylium ion **15**, which is attacked by the proximal nitrogen nucleophile to form **16**. Loss of the rhodium carboxylate produces the benzazepinone product. Alternatively, the key [1,2] migration step could

DOI: 10.1021/jacs.7b01833
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

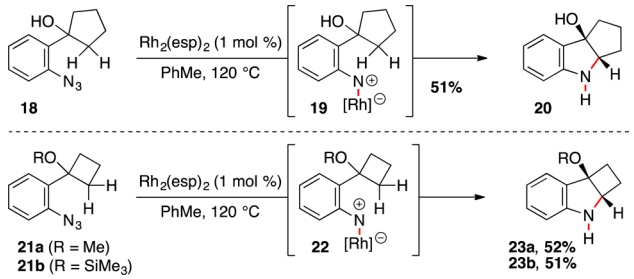
Scheme 2. Possible Mechanism for Rh_2(II)-Catalyzed Benzazepinone Formation



occur at the same time as loss of dinitrogen: coordination of the rhodium carboxylate to the γ-nitrogen in **17** activates the substrate for a semipinacol ring expansion with concomitant loss of N_2 to produce **13**.[22]

Support for a mechanism via a rhodium *N*-aryl nitrene was obtained from the reactivity of aryl azides **18** and **21** (Scheme 3). To assay the importance of ring-strain to the success of the

Scheme 3. Mechanistic Support for the Intermediacy of a Rhodium *N*-Aryl Nitrene



reaction, *o*-cyclopentanol-substituted aryl azide **18** was constructed from *N*-phenyl-*tert*-butyl carbamate following the route outline in Table 1 using cyclopentanone in place of cyclobutanone. Instead of ring expansion, submission of **18** to the reaction conditions resulted in sp^3-C−H bond amination to produce indoline **20** as the only product. The formation of the amination product implicates the intermediacy of rhodium *N*-aryl nitrene **19** since these species are established to react with C−H bonds.[6] The reactivity of aryl azides **21** revealed the importance of hydroxyl group for ring-expansion process. When it was replaced with either a methyloxy or trimethylsilyloxy group, C−H bond amination occurred instead to produce indolines **23** as the only product. The formation of indolines **23** from *o*-cyclobutyl-substituted aryl azides **21** not only implicate rhodium *N*-aryl nitrene **22** but also show the competitiveness of C−H bond amination to other potential ring-expansion processes.

A Rh_2(II)-catalyzed reaction of *o*-cyclobutanol-substituted aryl azides was discovered to afford medium-ring *N*-heterocycles. This domino reaction is triggered by formation of the rhodium *N*-aryl nitrene, which unravels the *o*-cyclobutanol substituent. Our investigations into the scope of the reaction reveal that the ring-expansion step of the catalytic cycle is both chemoselective and stereospecific to enable predictable formation of a broad range of benzazepinones. Future experiments will be aimed at exploring the reactivity of the strained indoline C−H bond amination product as well as developing domino reaction sequences to access more complex medium-ring *N*-heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b01833.

Experimental procedures; spectroscopic and analytical data for the products (PDF)
X-ray crystallographic data for **9c** (CIF)
X-ray crystallographic data for **11j** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*tgd@uic.edu

ORCID

Tom G. Driver: 0000-0001-7001-342X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Science Foundation CHE-1564959, University of Illinois at Chicago, Office of the Vice-Chancellor for Research, Huaqiao University Xiamen, and the Fujian Hundred Talents Plan for their generous financial support.

■ REFERENCES

(1) (a) Wender, P. A. *Chem. Rev.* **1996**, *96*, 1. (b) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40. (c) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010. (d) Wender, P. A.; Quiroz, R. V.; Stevens, M. C. *Acc. Chem. Res.* **2015**, *48*, 752. (e) Micalizio, G. C.; Hale, S. B. *Acc. Chem. Res.* **2015**, *48*, 663.

(2) For reviews, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (c) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551. (d) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (e) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341. (f) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676. (g) Spencer, W. T., III; Vaidya, T.; Frontier, A. J. *Eur. J. Org. Chem.* **2013**, *2013*, 3621. (h) Jana, N.; Driver, T. G. *Org. Biomol. Chem.* **2015**, *13*, 9720.

(3) For reviews of the reactions of azides toward transition metal catalysts, see: (a) Katsuki, T. *Chem. Lett.* **2005**, *34*, 1304. (b) Cenini, S.; Gallo, E.; Caselli, A.; Ragaini, F.; Fantauzzi, S.; Piangiolino, C. *Coord. Chem. Rev.* **2006**, *250*, 1234. (c) Driver, T. G. *Org. Biomol. Chem.* **2010**, *8*, 3831. (d) Lu, H.; Zhang, X. P. *Chem. Soc. Rev.* **2011**, *40*, 1899. (e) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040.

(4) For leading reports of transition-metal-catalyzed N-atom-transfer reactions from azides, see: (a) Kwart, H.; Khan, A. A. *J. Am. Chem. Soc.* **1967**, *89*, 1951. (b) Bach, T.; Körber, C. *Tetrahedron Lett.* **1998**, *39*, 5015. (c) Cenini, S.; Tollari, S.; Penoni, A.; Cereda, C. *J. Mol. Catal. A: Chem.* **1999**, *137*, 135. (d) Cenini, S.; Gallo, E.; Penoni, A.; Ragaini, F.; Tollari, S. *Chem. Commun.* **2000**, 2265. (e) Bach, T.; Körber, C. *J. Org. Chem.* **2000**, *65*, 2358. (f) Badiei, Y. M.; Dinescu, A.; Dai, X.; Palomino, R. M.; Heinemann, F. W.; Cundari, T. R.; Warren, T. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9961. (g) Lu, H.; Subbarayan, V.; Tao, J.; Zhang, X. P. *Organometallics* **2010**, *29*, 389. (h) Lu, H.; Jiang, H.;

DOI: 10.1021/jacs.7b01833
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Wojtas, L.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 10192. (i) Lyaskovskyy, V.; Suarez, A. I. O.; Lu, H.; Jiang, H.; Zhang, X. P.; de Bruin, B. *J. Am. Chem. Soc.* **2011**, *133*, 12264. (j) Tang, C.; Jiao, N. *J. Am. Chem. Soc.* **2012**, *134*, 18924. (k) Nishioka, Y.; Uchida, T.; Katsuki, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 1739. (l) Hennessy, E. T.; Betley, T. A. *Science* **2013**, *340*, 591. (m) Shin, K.; Baek, Y.; Chang, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 8031. (n) Hennessy, E. T.; Liu, R. Y.; Iovan, D. A.; Duncan, R. A.; Betley, T. A. *Chem. Sci.* **2014**, *5*, 1526. (o) Shin, K.; Ryu, J.; Chang, S. *Org. Lett.* **2014**, *16*, 2022. (p) Jiang, H.; Lang, K.; Lu, H.; Wojtas, L.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 11604. (q) Lu, H.; Lang, K.; Jiang, H.; Wojtas, L.; Zhang, X. P. *Chem. Sci.* **2016**, *7*, 6934.

(5) Cf.: (a) Nguyen, Q.; Sun, K.; Driver, T. G. *J. Am. Chem. Soc.* **2012**, *134*, 7262. (b) Pumphrey, A. L.; Dong, H.; Driver, T. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 5920. (c) Jones, C.; Nguyen, Q.; Driver, T. G. *Angew. Chem., Int. Ed.* **2014**, *53*, 785.

(6) (a) Harrison, J. G.; Gutierrez, O.; Jana, N.; Driver, T. G.; Tantillo, D. J. *J. Am. Chem. Soc.* **2016**, *138*, 487. (b) Kong, C.; Jana, N.; Jones, C.; Driver, T. G. *J. Am. Chem. Soc.* **2016**, *138*, 13271.

(7) For reviews of reactions triggered by strain relief, see: (a) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485. (b) Leemans, E.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2011**, *111*, 3268. (c) Walczak, M. A. A.; Krainz, T.; Wipf, P. *Acc. Chem. Res.* **2015**, *48*, 1149.

(8) For recent, leading reports on the ring opening of cyclobutanols, see: (a) Seiser, T.; Cramer, N. *J. Am. Chem. Soc.* **2010**, *132*, 5340. (b) Zhao, H.; Fan, X.; Yu, J.; Zhu, C. *J. Am. Chem. Soc.* **2015**, *137*, 3490. (c) Ren, R.; Wu, Z.; Xu, Y.; Zhu, C. *Angew. Chem., Int. Ed.* **2016**, *55*, 2866. (d) Guo, J.-J.; Hu, A.; Chen, Y.; Sun, J.; Tang, H.; Zuo, Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 15319.

(9) Cf.: (a) Wojciechowski, K. *Eur. J. Org. Chem.* **2001**, *2001*, 3587. (b) Lee, A.; Younai, A.; Price, C. K.; Izquierdo, J.; Mishra, R. K.; Scheidt, K. A. *J. Am. Chem. Soc.* **2014**, *136*, 10589.

(10) Cf.: (a) Thornton, A. R.; Blakey, S. B. *J. Am. Chem. Soc.* **2008**, *130*, 5020. (b) Thornton, A. R.; Martin, V. I.; Blakey, S. B. *J. Am. Chem. Soc.* **2009**, *131*, 2434. (c) Lu, H.; Tao, J.; Jones, J. E.; Wojtas, L.; Zhang, X. P. *Org. Lett.* **2010**, *12*, 1248. (d) Adams, C. S.; Boralsky, L. A.; Guzei, I. A.; Schomaker, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 10807.

(11) Fensome, A.; Grubb, G.; Harrison, D. D.; Winneker, R. C.; Zhang, P.; Kern, J. C.; Terefenko, E. A. (Wyeth, John, and Brother Ltd.). Patent WO2004000801A2, 2003.

(12) (a) Barral, K.; Moorhouse, A. D.; Moses, J. E. *Org. Lett.* **2007**, *9*, 1809. (b) Zhang, F.; Moses, J. E. *Org. Lett.* **2009**, *11*, 1587.

(13) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378.

(14) (a) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 7558. (b) Kornecki, K. P.; Berry, J. F. *Chem. - Eur. J.* **2011**, *17*, 5827.

(15) Nguyen, Q.; Nguyen, T.; Driver, T. G. *J. Am. Chem. Soc.* **2013**, *135*, 620.

(16) (a) Badiei, Y. M.; Krishnaswamy, A.; Melzer, M. M.; Warren, T. H. *J. Am. Chem. Soc.* **2006**, *128*, 15056. (b) Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey, A. L.; Driver, T. G. *Org. Lett.* **2007**, *9*, 5191.

(17) Shou, W. G.; Li, J.; Guo, T.; Lin, Z.; Jia, G. *Organometallics* **2009**, *28*, 6847.

(18) (a) Ragaini, F.; Penoni, A.; Gallo, E.; Tollari, S.; Gotti, C. L.; Lapadula, M.; Mangioni, E.; Cenini, S. *Chem. - Eur. J.* **2003**, *9*, 249. (b) Caselli, A.; Gallo, E.; Fantauzzi, S.; Morlacchi, S.; Ragaini, F.; Cenini, S. *Eur. J. Inorg. Chem.* **2008**, *2008*, 3009.

(19) Sun, K.; Sachwani, R.; Richert, K. J.; Driver, T. G. *Org. Lett.* **2009**, *11*, 3598.

(20) See the Supporting Information for the conditions screened.

(21) To date, our efforts to generate *N*-alkyl metal nitrenes from alkyl azides and control their reactivity have produced only decomposition.

(22) (a) Liu, H. J.; Ogino, T. *Tetrahedron Lett.* **1973**, *14*, 4937. (b) Whitesell, J. K.; Minton, M. A.; Flanagan, W. G. *Tetrahedron* **1981**, *37*, 4451.

(23) (a) Cundari, T. R.; Morello, G. R. *J. Org. Chem.* **2009**, *74*, 5711. (b) Harrold, N. D.; Waterman, R.; Hillhouse, G. L.; Cundari, T. R. *J. Am. Chem. Soc.* **2009**, *131*, 12872. (c) Tekarli, S. M.; Williams, T. G.; Cundari, T. R. *J. Chem. Theory Comput.* **2009**, *5*, 2959.

(24) For a cyclobutanol ring expansion involving a putative electrophilic carbene intermediate, see: Falck, J. R.; He, A.; Reddy, L. M.; Kundu, A.; Barma, D. K.; Bandyopadhyay, A.; Kamila, S.; Akella, R.; Bejot, R.; Mioskowski, C. *Org. Lett.* **2006**, *8*, 4645.

DOI: 10.1021/jacs.7b01833
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX