J|A|C|S
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Rh_2(II)-Catalyzed Intramolecular Aliphatic C–H Bond Amination Reactions Using Aryl Azides as the N-Atom Source

Quyen Nguyen, Ke Sun, and Tom G. Driver*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061, United States

Supporting Information

ABSTRACT: Rhodium(II) dicarboxylate complexes were discovered to catalyze the intramolecular amination of unactivated primary, secondary, or tertiary aliphatic C–H bonds using aryl azides as the N-atom precursor. While a strong electron-withdrawing group on the nitrogen atom is typically required to achieve this reaction, we found that both electron-rich and electron-poor aryl azides are efficient sources for the metal nitrene reactive intermediate.

The development of transition metal-catalyzed aliphatic C–H bond amination reactions that are stereoselective, use readily accessible starting materials and catalysts, and are environmentally benign continues to inspire the efforts of research groups around the world.[1,2] While considerable progress has been made, the current methods are still limited by the oxidative conditions to form the nitrene and the requirement for strong electron-withdrawing groups on the nitrene (Scheme 1). The use of azides as the N-atom source would address these limitations because no oxidant would be required and the only byproduct of the reaction would the environmentally benign N_2 gas.[3] While azides have been used for a variety of N-atom-transfer reactions,[2b,4] these transformations also require electron-withdrawing groups on the azide. We anticipated that a more general, complementary solution for aliphatic C–H bond amination might emerge if conditions were found to use electron-neutral aryl azides as the N-atom source. While we have reported a number of sp^2 C–H bond amination reactions using aryl azides,[5] our mechanism studies suggest that C–N bond formation occurs via a 4π-electron-5-atom electrocyclization.[5b] In contrast, aliphatic C–H bond amination requires metal-catalyzed C–H insertion or H-atom abstraction mechanisms—processes that have remained elusive to control using aryl azides as the N-atom source.[6]

Scheme 1. Nitrogen Substituent Requirements for Aliphatic C–H Bond Amination

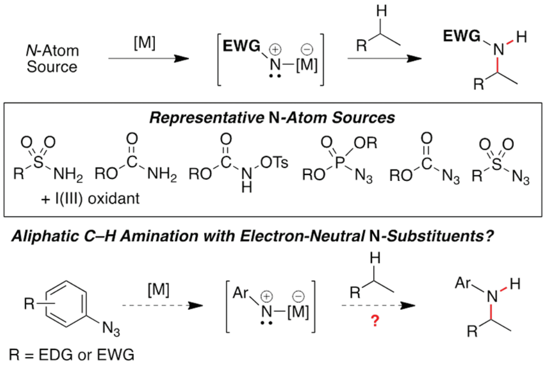
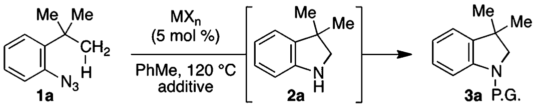


Table 1. Development of Optimal Conditions



entry	catalyst	additive	conv, %[a]	yield, %[b]
1	none	n.a.	0	0
2	$FeBr_2$	n.a.	0	dec[c]
3	CuBr	n.a.	0	0
4	CoTPP	n.a.	0	0
5	$RuCl_3 \cdot nOH_2$	n.a.	0	0
6	$[Ir(cod)OMe]_2$	n.a.	0	0
7	$[Rh(cod)OMe]_2$	n.a.	10	0[c]
8	$Rh_2(O_2CC_7H_{15})_4$	n.a.	35	35
9	$Rh_2(esp)_2$	n.a.	99	75
10	$Rh_2(esp)_2$	Boc_2O	99	90
11	$Rh_2(esp)_2$	Ac_2O	99	83
12	$Rh_2(esp)_2$	Bz_2O	99	aniline
13	$Rh_2(esp)_2$	Tf_2O	99	aniline

[a] As determined using ^1H NMR spectroscopy. [b] Isolated after silica gel chromatography. [c] Aniline formed.

In search of the optimal conditions to achieve intramolecular aliphatic C–H bond amination using aryl azides, the reactivity of *o-tert*-butylaryl azide **1a** toward transition metal complexes was examined (Table 1).[7] This aryl azide is relatively thermally robust, with no reaction observed at 120 °C (entry 1).[8] Exposure of **1a** to commercially available transition metal complexes known to catalyze N-atom-transfer reactions was met with limited success. Indoline **3a** was not observed in the presence of iron,[9] copper,[10] cobalt,[2b,4a−c] ruthenium,[2a,6,11] or iridium[12] complexes (entries 2–6). Partial conversion to indoline **2** was observed when rhodium octanoate was used (entry 8). We anticipated that the partial conversions resulted from catalyst decomposition, and we found that using more thermally robust $Rh_2(esp)_2$[13] improved both the conversion and yield of the process (entry 9). Examination of alternative solvents, concentration, and temperatures, however, did not

Received: February 15, 2012
Published: April 21, 2012

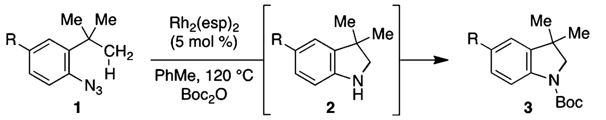
dx.doi.org/10.1021/ja301519q | J. Am. Chem. Soc. 2012, 134, 7262–7265

increase the yield, and control experiments revealed that oxidative decomposition of the indoline occurred during purification.

To improve the isolated yield of the amination reaction, in situ protection of the nitrogen atom was attempted. In line with our assumption, we found that the reaction yield was improved when the indoline was protected with either a Boc or Ac group (entries 10 and 11). The reaction outcome appeared to correlate with the pK_a of the acid byproduct of the protection reaction: aniline was produced when the stronger benzoic and triflic acids were produced (entries 12 and 13).[14]

Using these optimal conditions, the electronic and steric constraints of the aliphatic C−H bond amination reaction were investigated (Table 2). In contrast to existing amination processes,[2,4] our method does not require an electron-withdrawing group on the nitrogen: aryl azides bearing *para*-electron-releasing, -neutral, or -withdrawing groups were converted to indolines. Illustrating the chemoselectivity of our process, olefins were tolerated as substituents (entry 5).

Table 2. Scope and Limitations of Indoline Formation

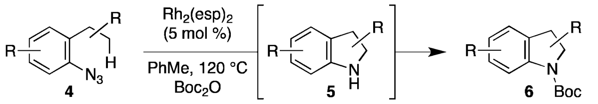


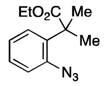
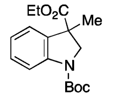
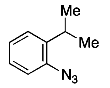
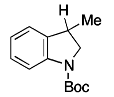
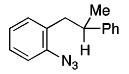
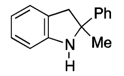
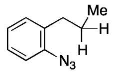
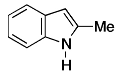
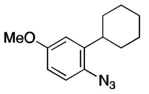
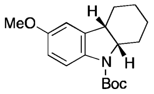
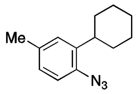
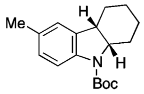
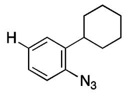
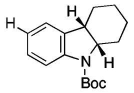
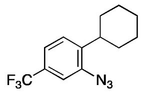
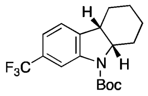
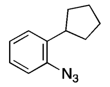
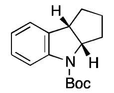
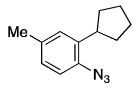
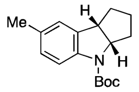
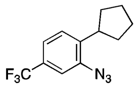
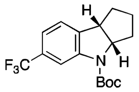
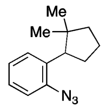
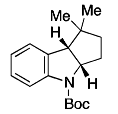
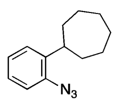
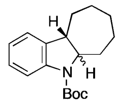
entry	1	R	yield, %^{a}
1	**1a**	H	84
2	**1b**	OMe	63
3	**1c**	Me	54
4	**1d**	CH_2CH_2Ph	64
5	**1e**	CHCHPh	70
6	**1f**	Ph	54
7	**1g**	3,5-$OMe_2C_6H_3$	58
8	**1h**	Br	73

[a] Isolated after silica gel chromatography.

To further examine the scope of the transformation, the identity of the *ortho*-alkyl substituent was varied (Table 3). While replacing one of the methyl groups with an ester group did not diminish the yield (entry 1), substitution with hydrogen reduced the reaction efficiency (entry 2). Amination can be achieved at tertiary and secondary C−H bonds, although dehydrogenation of **5d** occurred to afford indole. Dehydrogenation could be circumvented if an additional substituent was introduced at the benzylic position on the aryl azide. Submission of **4e**−**4k** to reaction conditions produced indolines as single diastereomers (entries 5−11). In contrast, pyrolysis of aryl azide **4g** was reported by Smolinsky to produce a 1:1 mixture of diastereomers.[15] Although reaction with the methyl C−H bond in azide **4l** could produce a six-membered ring, only amination of the methyl C−H bond was observed to afford indoline **5l** as the sole product. While single diastereomers were obtained from substrates bearing *o*-cyclopentyl or cyclohexyl groups, diminished stereoselectivity was observed with *o*-cycloheptyl-substituted aryl azide **4m** (entry 13).

Table 3. Scope and Limitations of Indoline Formation

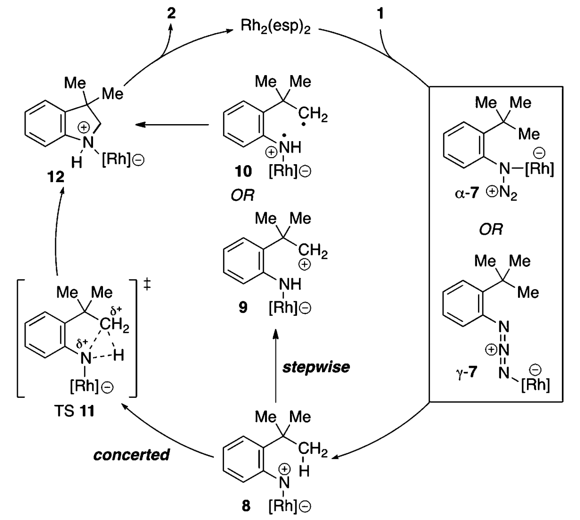


entry	4	aryl azide	indoline	yield, %^{a}
1	**a**			70
2	**b**			20
3	**c**			55^{b}
4	**d**			30^{c}
5	**e**			80
6	**f**			73
7	**g**			70
8	**h**			63
9	**i**			85
10	**j**			73
11	**k**			82
12	**l**			86
13	**m**			63 d.r. 82:18

[a] Isolated after silica gel chromatography. [b] 20% aniline observed. [c] 30% aniline observed.

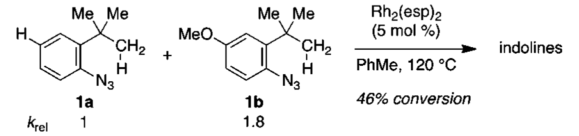
While indoline formation could occur through several different mechanisms,[10a,16] our reactivity trends suggest that C−N bond formation occurs through N-atom transfer (Scheme 2). Coordination of the rhodium(II) carboxylate to either the α- or γ-nitrogen of the aryl azide produces **7**.[17] Extrusion of N_2 then forms the rhodium nitrene **8**.[18] While rhodium could mediate a reversible one-electron oxidation to generate free nitrene,[19] our current mechanistic hypothesis is that the nitrene remains metal bound for the C−H bond amination step since pyrolysis involving free nitrene is not diastereoselective.[15] The mechanism of the amination step could be stepwise or concerted: hydride[20] or H-atom abstraction[16a,21] (to form **9** or **10**) followed by recombination produces the C−N bond; alternatively this bond could be formed through the concerted

Scheme 2. Possible Mechanisms for Intramolecular Aliphatic C−H Bond Amination from Aryl Azides



insertion[16c,22] of the metal nitrene into the proximal C−H bond via transition state **11**. Finally, the indoline is produced upon dissociation of the rhodium complex from **12**.

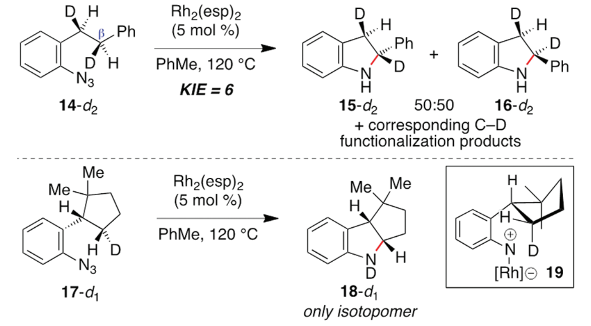
Insight into the initial steps of the catalytic cycle was provided by the reactivity of 4-substituted aryl azides toward reaction conditions (eq 1). Underscoring the difference between our method for aliphatic C−H bond amination and others, we found that more electron-rich aryl azides (e.g., **1b**) were more reactive to the reaction conditions. The increased reactivity of **1b** relative to **1a** could be due to either preferred coordination of **1b** to $Rh_2(esp)_2$ or an accelerated N_2 extrusion from the resulting azide−metal complex **7**.



(1)

To examine the nature of the C−H bond cleavage step, two-labeled aryl azides were examined (Scheme 3). We anticipated that the number of indoline diastereomers from **14**-d_2 would reveal if the mechanism of C−H bond amination was stepwise or concerted. If the reaction was concerted, insertion into either the β-C−H or β-C−D bond would produce only two products. In contrast, if a radical (or cation) was formed at the β-carbon, then scrambling of the C2-stereocenter could occur before recombination to form both **15**-d_2 and **16**-d_2. In support of a stepwise C−H bond amination, two diastereomers of 2-phenylindoline (dr 50:50) and an intramolecular kinetic isotope effect (KIE) of 6.7 were observed.[23] The magnitude of this isotope effect is significantly smaller than for reactions involving an H-atom abstraction by an aryl nitrene[21] or an aryl metal nitrene[6c] (k_H/k_D = 12−14), but larger than hydride shift reactions ($k_H/k_D \approx 2$ for Cannizzaro reaction and Meerwein−Ponndorf−Verley reduction).[24−26] Smaller KIEs were observed at lower reaction temperatures, revealing that our amination reaction occurs above the isokinetic temperature and, as a consequence, is under entropic control.[27,28] We found, however, that the spatial constraints of this reaction override these isotope effects: cyclopentanone-derived aryl azide **17**-d_1 reacted preferentially with the *syn*-C−D bond to form **18** exclusively.[29]

Scheme 3. Isotope Labeling Studies



In conclusion, we have developed an efficient and diastereoselective rhodium(II)-catalyzed aliphatic C−H bond amination reaction that uses an aryl azide as the N-atom source. Our method distinguishes itself from previously reported aliphatic C−H bond amination reactions by not requiring a strong electron-withdrawing group on the nitrogen atom. The reactivity of stereospecific labeled aryl azides revealed that the amination reaction occurred stepwise with the *syn*-C−H bond. Our current aims are to more deeply examine the nature of the catalytic intermediates in this C−H bond amination reaction and to extend this newfound reactivity of aryl azides to the stereoselective synthesis of complex, functionalized *N*-heterocycles.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectroscopic and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

tgd@uic.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Institutes of Health NIGMS (R01GM084945) and the University of Illinois at Chicago for their generous financial support. We thank Mr. Furong Sun (UIUC) for high-resolution mass spectrometry data.

■ REFERENCES

(1) For recent reviews, see: (a) Du Bois, J. *Org. Process Res. Dev.* **2011**, *15*, 758. (b) Davies, H. M. L.; Du Bois, J.; Yu, J.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1855. (c) Stokes, B. J.; Driver, T. G. *Eur. J. Org. Chem.* **2011**, 4071. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061.

(2) Cf.: (a) Harvey, M. E.; Musaev, D. G.; Du Bois, J. *J. Am. Chem. Soc.* **2011**, *133*, 17207. (b) Lu, H.; Tao, J.; Jones, J. E.; Wojtas, L.; Zhang, X. P. *Org. Lett.* **2010**, *12*, 1248. (c) Kurokawa, T.; Kim, M.; Bois, J. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 2777. (d) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (e) Huard, K.; Lebel, H. *Chem.—Eur. J.* **2008**, *14*, 6222. (f) Liang, C.; Collet, F.; Robert-Peillard, F.; Müller, P.; Dodd, R. H.; Dauban, P. *J. Am. Chem. Soc.* **2008**, *130*, 343. (g) Li, Z.; Capretto, D. A.; Rahaman, R.; He, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 5184.

(3) For reviews, see: (a) Driver, T. G. *Org. Biomol. Chem.* **2010**, *8*, 3831. (b) Cenini, S.; Gallo, E.; Caselli, A.; Ragaini, F.; Fantauzzi, S.; Piangiolino, C. *Coord. Chem. Rev.* **2006**, *250*, 1234. (c) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188. (d) Katsuki, T. *Chem. Lett.* **2005**, *34*, 1304.

(4) Cf.: (a) Subbarayan, V.; Ruppel, J. V.; Zhu, S.; Perman, J. A.; Zhang, X. P. *Chem. Commun.* **2009**, 4266. (b) Gao, G.-Y.; Lu, H.; Subbarayan, V.; Tao, J.; Zhang, X. P. *Organometallics* **2009**, *29*, 389. (c) Ruppel, J. V.; Jones, J. E.; Huff, C. A.; Kamble, R. M.; Chen, Y.; Zhang, X. P. *Org. Lett.* **2008**, *10*, 1995. (d) Jones, J. E.; Ruppel, J. V.; Gao, G.-Y.; Moore, T. M.; Zhang, X. P. *J. Org. Chem.* **2008**, *73*, 7260. (e) Kawabata, H.; Omura, K.; Uchida, T.; Katsuki, T. *Chem.—Asian J.* **2007**, *2*, 248. (f) Kawabata, H.; Omura, K.; Katsuki, T. *Tetrahedron Lett.* **2006**, *47*, 1571.

(5) (a) Dong, H.; Latka, R. T.; Driver, T. G. *Org. Lett.* **2011**, *13*, 2726. (b) Stokes, B. J.; Richert, K. J.; Driver, T. G. *J. Org. Chem.* **2009**, *74*, 6442. (c) Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey, A. L.; Driver, T. G. *Org. Lett.* **2007**, *9*, 5191. (d) Shen, M.; Leslie, B. E.; Driver, T. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5056. (e) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500.

(6) For descriptions of the competing reactions, see: (a) Caselli, A.; Gallo, E.; Ragaini, F.; Ricatto, F.; Abbiati, G.; Cenini, S. *Inorg. Chim. Acta* **2006**, *359*, 2924. (b) Ragaini, F.; Penoni, A.; Gallo, E.; Tollari, S.; Gotti, C. L.; Lapadula, M.; Mangioni, E.; Cenini, S. *Chem.—Eur. J.* **2003**, *9*, 249. (c) Cenini, S.; Tollari, S.; Penoni, A.; Cereda, C. *J. Mol. Catal. A* **1999**, *137*, 135.

(7) Refer to the Supporting Information for a comprehensive description of the reaction conditions examined.

(8) Photolysis or pyrolysis of aryl azides with *ortho*-alkyl substituents affords a variety of products, including tar, anilines, azepines, indoles, and indolines. For leading reports, see: (a) Murata, S.; Yoshidome, R.; Satoh, Y.; Kato, N.; Tomioka, H. *J. Org. Chem.* **1995**, *60*, 1428. (b) Smolinsky, G.; Feuer, B. I. *J. Org. Chem.* **1964**, *29*, 3097.

(9) For recent reports of iron-catalyzed aliphatic C−H bond amination from azides, see: (a) King, E. R.; Hennessy, E. T.; Betley, T. A. *J. Am. Chem. Soc.* **2011**, *133*, 4917. (b) King, E. R.; Betley, T. A. *Inorg. Chem.* **2009**, *48*, 2361.

(10) For recent reports of copper-catalyzed aliphatic C−H bond amination from azides, see: (a) 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. (b) Badiei, Y. M.; Krishnaswamy, A.; Melzer, M. M.; Warren, T. H. *J. Am. Chem. Soc.* **2006**, *128*, 15056.

(11) For reports of Ru-catalyzed amination, see: (a) Milczek, E.; Boudet, N.; Blakey, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6825. (b) Shou, W. G.; Li, J.; Guo, T.; Lin, Z.; Jia, G. *Organometallics* **2009**, *28*, 6847.

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

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

(14) Azepines, common aryl nitrene byproducts, were never observed for any of the substrates investigated. In general, the only byproduct observed in our Rh$_2$(II)-catalyzed amination reaction was aniline.

(15) Smolinsky, G. *J. Am. Chem. Soc.* **1961**, *83*, 2489.

(16) For leading reports on the mechanism of related metal-mediated C−H bond amination reactions, see: (a) Lyaskovskyy, V.; Suarez, A. I. O.; Lu, H.; Jiang, H.; Zhang, X. P.; de Bruin, B. *J. Am. Chem. Soc.* **2011**, *133*, 12264. (b) Fiori, K. W.; Espino, C. G.; Brodsky, B. H.; Du Bois, J. *Tetrahedron* **2009**, *65*, 3042. (c) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 562.

(17) For crystal structures of metal−azide complexes, see: (a) Waterman, R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2008**, *130*, 12628. (b) Dias, H. V. R.; Polach, S. A.; Goh, S.-K.; Archibong, E. F.; Marynick, D. S. *Inorg. Chem.* **2000**, *39*, 3894. (c) Fickes, M. G.; Davis, W. M.; Cummins, C. C. *J. Am. Chem. Soc.* **1995**, *117*, 6384. (d) Proulx, G.; Bergman, R. G. *J. Am. Chem. Soc.* **1995**, *117*, 6382.

(18) For computational studies on the mechanism of metal nitrenoid formation from azides, see: (a) References 10a and 16a. (b) Cundari, T. R.; Dinescu, A.; Kazi, A. B. *Inorg. Chem.* **2008**, *47*, 10067.

(19) Kornecki, K. P.; Berry, J. F. *Chem.—Eur. J.* **2011**, *17*, 5827.

(20) Cf.: (a) Vadola, P. A.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 16525. (b) Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226.

(21) Murata, S.; Tsubone, Y.; Kawai, R.; Eguchi, D.; Tomioka, H. *J. Phys. Org. Chem.* **2005**, *18*, 9.

(22) (a) Lin, X.; Zhao, C.; Che, C.-M.; Ke, Z.; Phillips, D. L. *Chem.—Asian J.* **2007**, *2*, 1101. (b) Nägeli, I.; Baud, C.; Bernardinelli, G.; Jacquier, Y.; Moraon, M.; Müller, P. *Helv. Chim. Acta* **1997**, *80*, 1087.

(23) The observed KIE is composed of both a primary and an assumed small secondary isotope effect. We thank a reviewer for pointing out that this secondary effect is not necessarily the same for the two diastereomeric transition states that lead to **15**-d_2 and **16**-d_2.

(24) (a) Wiberg, K. B. *J. Am. Chem. Soc.* **1954**, *76*, 5371. (b) Cohen, R.; Graves, C. R.; Nguyen, S. T.; Martin, J. M. L.; Ratner, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 14796.

(25) $k_H/k_D = 5$ was reported by Lebel and Huard for the Rh$_2$(II)-catalyzed C−H bond amination of cyclohexane using *N*-tosyloxycarbamate as the N-atom source.[2e]

(26) If C−H bond cleavage did occur via a hydride shift, formation of carbocation **9** would be expected to trigger the migration of one of the methyl groups. For alkyl group migrations in Rh$_2$(II)-catalyzed reactions of aryl azides, see: Sun, K.; Liu, S.; Bec, P. M.; Driver, T. G. *Angew. Chem., Int. Ed.* **2011**, *50*, 1702.

(27) At 100 and 80 °C, the KIE was determined to be 5.7 and 3.7. The linear correlation of these data with temperature revealed the isokinetic temperature to be 43 °C.

(28) For leading discussions on the isokinetic temperature, see: (a) Carpenter, B. K. *Determination of Organic Reaction Mechanisms*; Wiley: New York, 1984; pp 149−150. (b) Leffler, J. E. *J. Org. Chem.* **1955**, *20*, 1202.

(29) In contrast, other aliphatic C−H bond functionalization reactions show a preference for equatorial C−H bonds: (a) Chen, K.; Eschenmoser, A.; Baran, P. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9705. (b) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783. (c) Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, *5*, 4823.