Organic Letters
Letter
pubs.acs.org/OrgLett

Hydroboration of Arynes Formed by Hexadehydro-Diels–Alder Cyclizations with N-Heterocyclic Carbene Boranes

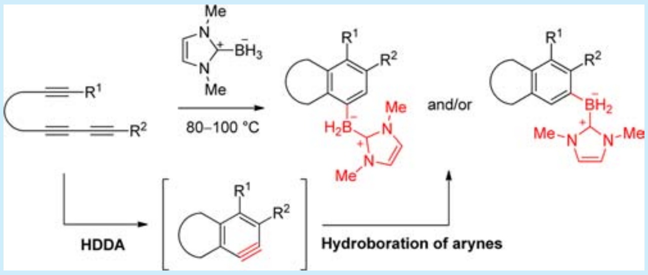
Takashi Watanabe,[†] Dennis P. Curran,*,[‡] and Tsuyoshi Taniguchi*,[†]

[†]School of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

[‡]Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States

Supporting Information

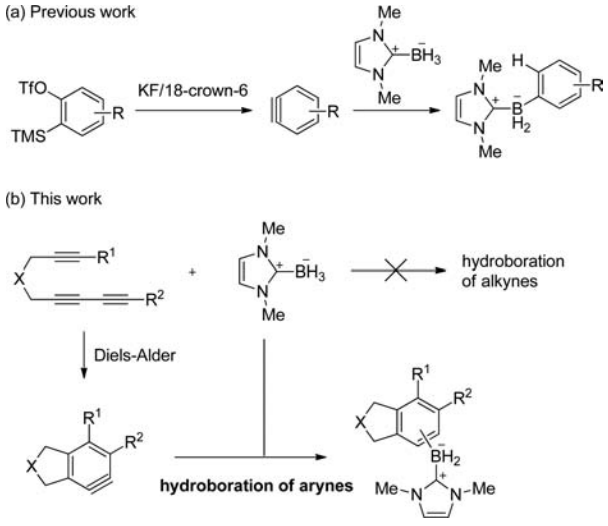
ABSTRACT: N-Heterocyclic carbene boranes (NHC-boranes) hydroborate arynes formed in situ by the hexadehydro-Diels–Alder (HDDA) reactions of triyne precursors. The reaction directly provides functionalized arylborane compounds. The unique feature of the NHC-boranes compared to other boranes is that they hydroborate only the aryne product and not the triyne precursor.



Arynes are reactive intermediates used for synthesis of various functionalized arenes.[1] Arynes often undergo nucleophilic additions or pericyclic reactions, and they participate in various transition-metal-catalyzed reactions.[1] Borylation of arynes is an attractive reaction because useful arylboron compounds would be formed. However, there are only a few metal-mediated borylations of arynes.[2,3]

Recently, we discovered that arynes are spontaneously hydroborated by N-heterocyclic carbene boranes (NHC-boranes).[4] Unlike most boranes, NHC-boranes are typically stable to air, moisture, and weak acids (Scheme 1).[5] Aryne hydroboration was suggested to occur by a leading hydride transfer from the NHC-borane to the aryne with B–Ar bond formation trailing. This directly produces the corresponding NHC-arylborane compounds.

Scheme 1. Hydroboration of Arynes



Arynes generally need to be generated from appropriate precursors in situ because they are transient species having strained alkynes. In the classical method of generation, 1,2-halobenzenes provide the corresponding arynes by 1,2-elimination with organometal reagents.[1] Today 2-(trimethylsilyl)phenyl trifluoromethanesulfonates are widely used aryne precursors because various arynes are formed under mild conditions with fluoride reagents.[6] This method was applied to the previous hydroboration study (Scheme 1).[4] Thermolysis of benzenediazonium-2-carboxylate derivatives and related methods are sometimes applied to aryne formation.[1]

The hexadehydro-Diels–Alder (HDDA) reaction of triyne compounds is a fundamentally different method for formation of arynes because the precursors are not 1,2-disubstituted arenes. Typically, heating triynes in appropriate solvents induces Diels–Alder cycloadditions to form intermediate arynes, which subsequently have opportunities to react with various potential partners. The HDDA reaction was independently reported by Johnson and Ueda in 1997.[7,8] Sterenberg reported the HDDA reaction using metal templates in 2009.[9] Recently, Hoye and Lee independently reported substantial extensions of this method.[10,11]

Generally, NHC-boranes do not cause hydroboration of alkenes or alkynes unless an acid or iodine is employed to form a catalyst.[12] Since NHC-ligands are strongly ligated to borane, NHC-boranes do not release borane (BH_3) even under heating. Therefore, we hypothesized that conducting HDDA reactions in the presence of NHC-boranes would provide borylated cycloaddition products via hydroboration of intermediary

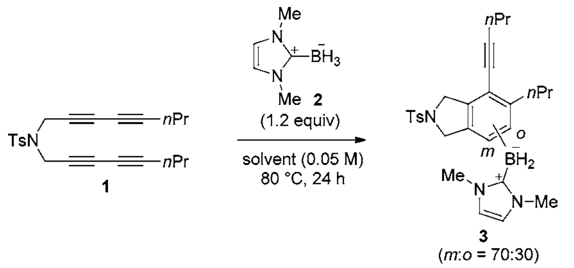
Received: May 21, 2015
Published: June 26, 2015

DOI: 10.1021/acs.orglett.5b01480
Org. Lett. 2015, 17, 3450–3453

arynes (Scheme 1). Here we report that heating of various triynes in the presence of NHC-boranes provides stable arylboranes in useful yields.

Table 1 shows selected results of preliminary reactions of tetrayne **1** (1.0 equiv) with dimethylimidazolylidene borane (**2**) (1.2 equiv). When these two compounds were heated in chloroform for 24 h at 80 °C, the target borylated isoindoline **3** was formed in 21% yield as a mixture of two regioisomers (*m*/*o*, 70:30) by NMR analysis of the crude product (entry 1). Changing the solvent improved the yield of **3**, with acetonitrile giving 30%, toluene giving 53%, and THF giving 55% (entries 2–4). The regioselectivity was similar in all four solvents.

Table 1. Reactions between Tetrayne 1 and NHC-Borane 2[a]



entry	solvent	yield (%)[b]
1	$CHCl_3$	21
2	MeCN	30
3	toluene	53
4	THF	55
5[c]	THF	18
6[d]	THF	70 (64)[e]

[a]Conditions (30 mg scale): **1** (0.079 mmol), **2** (0.095 mmol), solvent (1.6 mL) for 24 h at 80 °C in a sealed tube. [b]Estimated by ^{1}H NMR analysis of the crude product with an internal standard (dimethyl sulfone). [c]The reaction was performed at 60 °C. [d]2 equiv (0.158 mmol) of **2** was used. [e]Isolated yield.

When the temperature in THF was decreased to 60 °C, the NMR yield decreased to 18% (entry 5). In contrast, when 2.0 equiv of NHC-borane **2** was used in THF at 80 °C, the NMR yield of **3** increased to 70% (entry 6) . Purification of this reaction product by silica gel chromatography afforded compound **3** as an inseparable mixture of regioisomers in 64% isolated yield. Previous reports suggested that a hydride attack to an *ortho*-position of the aryne would give the *meta*-isomer as a major isomer based on a distortion model.[10,11,13]

Reactions of other NHC-boranes with tetrayne **1** were next tested under the conditions of Table 1, entry 6 (2 equiv NHC-borane, THF, 80 °C, 24 h). As shown in Figure 1, dimethyltriazolylidene-, tetramethylimidazolylidene-, dimethylbenzimidazolylidene-, and diisopropylimidazolylidene-boranes provided the corresponding arylboranes **4**–**7** in isolated yields ranging from 50% to 72%. Modest *meta*-selectivity was observed with these substrates (*m*/*o*, 60:40–75:25). Reaction with the bulky dipp-imidazolylidene borane (dipp is 2,6-diisopropylphenyl) gave **8** in 34% yield, now as a 50/50 mixture of regioisomers. All of the products are stable, easy to handle compounds.

Standard boranes will hydroborate **1** directly, so they are not viable reagents for this reaction. When a trimethylamine-borane complex (Me_3N-BH_3) was heated with tetrayne **1**, a complex reaction product was formed that may have contained a trace of the arylborane compound. It is likely that this complex can form Me_3N and BH_3 under the conditions of the HDDA reaction, hence the poor result. Accordingly, most boranes and borane complexes seem to be incompatible with the HDDA reaction precursors and conditions.

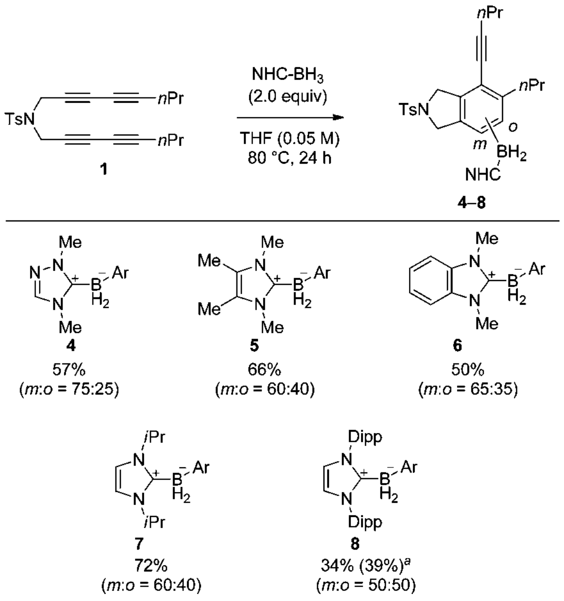


Figure 1. Results in reactions of tetrayne **1** with several NHC-boranes. Yields are based on isolated products. Ratios in parentheses are estimated by ^{1}H NMR analysis of the crude product. [a] The reaction was performed in toluene.

Figure 2 shows the results of reactions of several typical substrates **9**–**16** for the HDDA reaction with NHC-borane **2**. An *ortho*-isomer of isoindoline product **17** was a major product in the reaction of tetrayne **9** having triethylsilyl groups (*m*/*o*, 25:75). Nucleophilic additions to 3-silyl arynes tend to occur on the *meta*-position,[11d,14] and regioselectivity in the reaction of **9** could also be controlled by either a steric or an electronic effect of the silyl group.

The reaction of tetrayne **10** having silyloxy methyl groups also gave an *ortho*-isomer as a main product of isoindoline compounds **18** (*m*/*o*, 30:70). Product yield and regioselectivity in these reactions did not seem to depend on the solvent similarly to the reaction of **1**. When tetrayne **11** having bulky *tert*-butyl groups was employed, exclusive production of *ortho*-isomer **19** was observed.[11c] Clearly, *ortho*-selective borylation in these reactions is because a hydride donation from NHC-borane **2** to an *ortho*-position was discouraged by steric repulsion.

The reaction of ether analog **12** provided the corresponding arylborane product **20** similar to that of **1**. However, malonate analog **13** did not give an expected product in heated THF. Fortunately, we found that the reaction in toluene readily provided the corresponding arylborane product **21**, though a higher temperature (100 °C) and a long reaction (120 h) time were required.[10f] Similarly, triyne **14** having an *N*-phenyl amide group caused hydroboration with NHC-borane **2** in toluene and gave lactam **22**. However, the reaction of an ester analog (not shown in Figure 2) did not provide expected borylated lactone, though various reaction conditions were tested.

When the reaction of tetrayne **15** having an ynamide moiety was conducted, hydroboration of the intermediary aryne with NHC-borane **2** occurred with perfect regioselectivity and provided indoline compound **23** as a single isomer. This trend

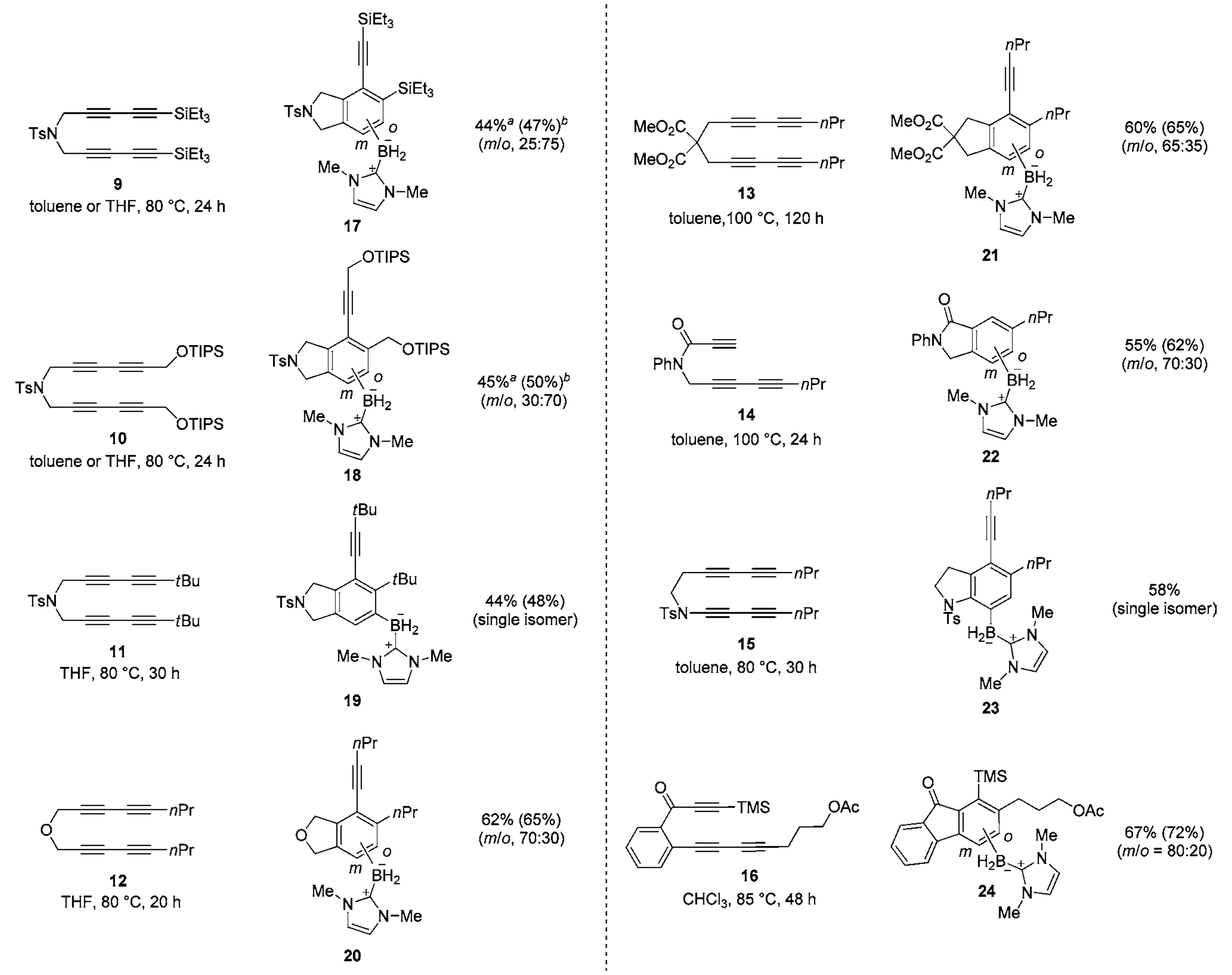


Figure 2. Reactions of several hexadehydro-Diels–Alder precursors with NHC-borane **2** (2.0 equiv) in a sealed tube (concentration was 0.05 M). Yields and ratios in parentheses were estimated by ^{1}H NMR analysis of the crude product with an internal standard (dimethyl sulfone or trioxane). [a] In toluene. [b] In THF.

is consistent with previous results in reactions of ynamide-type tetraynes.[11] The reaction of triyne **16** with NHC-borane **2** gave a good result in chloroform and produced the corresponding fluorenone compound **24** having a borane component in relatively good yield and regioselectivity.

In conclusion, we learned that arynes formed by the hexadehydro-Diels–Alder (HDDA) reaction of triynes are spontaneously hydroborated by NHC-boranes. The products, relatively complex aryl-substituted NHC-boranes, are easy to isolate and characterize and are stable to storage. Key to this success is that the NHC-boranes are compatible with the starting triynes, which are hydroborated directly by most other kinds of boranes. The ability to quickly make borylated products extends the growing synthetic utility of the HDDA reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and NMR spectra for isolated products are available in the Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01480.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: curran@pitt.edu.
*E-mail: tsuyoshi@p.kanazawa-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT). DPC thanks the US National Science Foundation for support.

■ REFERENCES

(1) Selected reviews on aryne chemistry: (a) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701–730. (b) Yoshida, H.; Ohshita, J.; Kunai, A. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 199–219. (c) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550–3577. (d) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140–3152. (e) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766–3778. (f) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191–218. (g) Goetz, A. E.; Shah, T. K.; Gard, N. K. *Chem. Commun.* **2015**, *51*, 34–45.

(2) Transition-metal-catalyzed diborylation of arynes: (a) Yoshida, H.; Okada, K.; Kawashima, S.; Tanino, K.; Ohshita, J. *Chem. Commun.* **2010**, *46*, 1763−1765. (b) Yoshida, H.; Kawashima, S.; Takemoto, Y.; Okada, K.; Ohshita, J.; Takaki, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 235−238.

(3) Borylzincation of arynes: Nagashima, Y.; Takita, R.; Yoshida, K.; Hirano, K.; Uchiyama, M. *J. Am. Chem. Soc.* **2013**, *135*, 18730−18733.

(4) Taniguchi, T.; Curran, D. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 13150−13154.

(5) Curran, D. P.; Solovyev, A.; Makhlouf Brahmi, M.; Fensterbank, L.; Malacria, M.; Lacôte, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 10294−10317.

(6) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, *12*, 1211−1214.

(7) (a) Bradley, A. Z.; Johnson, R. *J. Am. Chem. Soc.* **1997**, *119*, 9917−9918. (b) Ajaz, A.; Bradley, A. Z.; Burrell, R. C.; Li, W. H. H.; Daoust, K. J.; Bovee, L. B.; DiRico, K. J.; Johnson, R. P. *J. Org. Chem.* **2011**, *76*, 9320−9328.

(8) (a) Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1997**, *38*, 3943−3946. (b) Ueda, I.; Sakurai, Y.; Kawano, T.; Wada, Y.; Futai, M. *Tetrahedron Lett.* **1999**, *40*, 319−322. (c) Miyawaki, K.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **2000**, *41*, 1447−1451. (d) Miyawaki, K.; Ueno, F.; Ueda, I. *Heterocycles* **2001**, *54*, 887−900. (e) Kimura, H.; Torikai, K.; Miyawaki, K.; Ueda, I. *Chem. Lett.* **2008**, *37*, 662−663.

(9) Tsui, J. A.; Strenberg, B. T. *Organometallics* **2009**, *28*, 4906−4908.

(10) (a) Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. *Nature* **2012**, *490*, 208−212. (b) Niu, D.; Willoughby, P. H.; Woods, B. P.; Baire, B.; Hoye, T. R. *Nature* **2013**, *501*, 531−534. (c) Niu, D.; Hoye, T. R. *Nat. Chem.* **2013**, *6*, 34−40. (d) Hoye, T. R.; Baire, B.; Wang, T. *Chem. Sci.* **2014**, *5*, 545−550. (e) Niu, D.; Wang, T.; Woods, B. P.; Hoye, T. R. *Org. Lett.* **2014**, *16*, 254−257. (f) Woods, B. P.; Baire, B.; Hoye, T. R. *Org. Lett.* **2014**, *16*, 4578−4581. (g) Willoughby, P. H.; Niu, D.; Wang, T.; Haj, M. K.; Cramer, C. J.; Hoye, T. R. *J. Am. Chem. Soc.* **2014**, *136*, 13657−13665. (h) Pogula, V. D.; Wang, T.; Hoye, T. R. *Org. Lett.* **2015**, *17*, 856−859.

(11) (a) Yun, S. Y.; Wang, K.-P.; Mamidipalli, P.; Lee, D. *J. Am. Chem. Soc.* **2013**, *135*, 4668−4671. (b) Karmakar, R.; Mamidipalli, P.; Yun, S. Y.; Lee, D. *Org. Lett.* **2013**, *15*, 1938−1941. Additions/Corrections: *Org. Lett.* **2014**, *16*, 1032. (c) Wang, K.-P.; Yun, S. Y.; Mamidipalli, P.; Lee, D. *Chem. Sci.* **2013**, *4*, 3205−3211. (d) Karmakar, R.; Yun, S. Y.; Wang, K.-P.; Lee, D. *Org. Lett.* **2014**, *16*, 6−9. (e) Lee, N.-K.; Yun, S. Y.; Mamidipalli, P.; Salzman, R. M.; Lee, D.; Zhou, T.; Xia, Y. *J. Am. Chem. Soc.* **2014**, *136*, 4363−4368. (f) Mamidipalli, P.; Yun, S. Y.; Wang, K.-P.; Zhou, T.; Xia, Y.; Lee, D. *Chem. Sci.* **2014**, *5*, 2362−2367.

(12) (a) Prokofjevs, A.; Boussonnière, A.; Li, L.; Bonin, H.; Lacôte, E.; Curran, D. P.; Vedejs, E. *J. Am. Chem. Soc.* **2012**, *134*, 12281−12288. (b) Pan, X.; Boussonnière, A.; Curran, D. P. *J. Am. Chem. Soc.* **2013**, *135*, 14433−14437. (c) Boussonnière, A.; Pan, X.; Geib, S. J.; Curran, D. P. *Organometallics* **2013**, *32*, 7445−7450.

(13) Recent theoretical studies on aryne chemistry: (a) Garr, A. N.; Luo, D.; Brown, N.; Cramer, C. J.; Buszek, K. R.; VanderVelde, D. *Org. Lett.* **2010**, *12*, 96−99. (b) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y. J.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 1267−1269. (c) Im, G.-Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *132*, 17933−17944. (d) Medina, J. M.; Mackey, J. L.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 15798−15805. (e) Liang, Y.; Hong, X.; Yu, P.; Houk, K. N. *Org. Lett.* **2014**, *16*, 5702−5705.

(14) (a) Ikawa, T.; Nishiyama, T.; Shigeta, T.; Mohri, S.; Morita, S.; Takayanagi, S.-i.; Terauchi, Y.; Morikawa, Y.; Takagi, A.; Ishikawa, Y.; Fujii, S.; Kita, Y.; Akai, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 5674−5677. (b) Bronner, S. M.; Mackey, J. L.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2012**, *134*, 13966−13969.