OL | Organic Letters

Letter

Cite This: Org. Lett. 2019, 21, 7837−7840

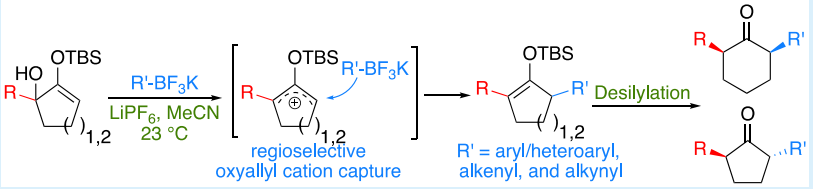
pubs.acs.org/OrgLett

Oxyallyl Cation Capture via Electrophilic Deborylation of Organoboronates: Access to α,α′-Substituted Cyclic Ketones

Truong N. Nguyen, Krit Setthakarn, and Jeremy A. May*

Department of Chemistry, University of Houston, 3585 Cullen Boulevard, Fleming Building Room 112, Houston, Texas 77204-5003, United States

Supporting Information

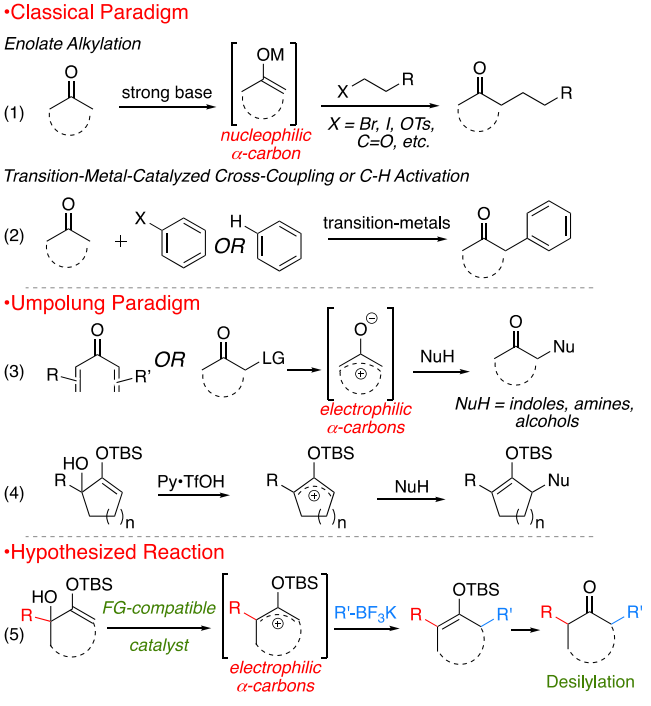


ABSTRACT: An umpolung strategy to synthesize α,α′-substituted cyclic ketones through the nucleophilic addition of organoboronates to α-hydroxyl silyl enol ethers is described. The reaction proceeds via the trapping of in situ generated oxyallyl cations via the electrophilic deborylation of C(sp^2) and C(sp) borates. This efficient and straightforward method provides direct access to α-substituted silyl enol ethers in high yield with complete regioselectivity. Desilylation in a one-pot procedure provides the corresponding α,α′-disubstituted ketones with high diastereoselectivity.

The carbonyl is among the most utilized functional groups for C−C bond formation in organic synthesis. The α-functionalization of carbonyls has long been pursued through the pregeneration or in situ formation of nucleophilic enols, enolates, or alkyl/silyl enol ethers and the subsequent reaction with carbon electrophiles (Scheme 1, eq 1). However, unsaturated electrophiles (alkenyl and aryl) are not viable in this approach. The transition-metal-catalyzed α-arylation of ketones offers an alternative to enolate alkylation (Scheme 1, eq 2).[1] However, these reactions require inert conditions and/or expensive ligands, and they often lack functional group tolerance for halogens and heterocycles. Herein is reported a robust strategy catalyzed by cationic lithium that is orthogonal to enolate alkylation and metal-based catalysis to effect the α-functionalization of α-hydroxy enol ethers with a wide range of sp^2 and sp carbon nucleophiles to access α,α′-disubstituted ketones.

Oxyallyl cations have recently been electrophilic partners in several C−C bond-forming strategies. These 2π-electron species have been used in (4 + 3) cycloadditions with dienes,[2] (3 + 2) cycloadditions with alkenes or alkynes,[3] and (3 + 3) cycloadditions with azides or nitrones,[4] providing diverse strategies for the construction of complex structures. Additionally, oxyallyl cations are intermediates in Nazarov cyclizations that have been intercepted by electron-rich π-nucleophiles both inter- and intramolecularly.[5] Recently, this umpolung reactivity has been utilized to synthesize α-functionalized ketones that are not accessible by traditional strategies. Elegant examples exist of the base-promoted in situ generation of oxyallyl cations from α-halo ketones or α-tosyloxyl ketones,[6] with an enantioselective process reported for the latter (Scheme 1, eq 3).[6c] Nonetheless, these seminal works solely utilized symmetric ketones. Unsymmetrical oxyallyl cations would be problematic due to the competitive addition at the α and α′ positions. The use of α-hydroxyl silyl enol ethers developed by Kartika and coworkers enabled the

Scheme 1. Strategies for α-Functionalization of Ketones



Received: August 9, 2019
Published: September 19, 2019

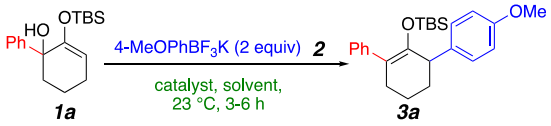
DOI: 10.1021/acs.orglett.9b02831
Org. Lett. 2019, 21, 7837−7840

regioselective addition of various carbon nucleophiles to generate α,α′-disubstituted silyl enol ethers, which could be subsequently converted into ketones (Scheme 1, eq 4).[7] Despite the advances mentioned above, the construction of ketones with unsaturated α-substitution via oxyallyl cation capture is still challenging, especially for ketones bearing α-alkene and α-alkyne substituents, even though such products are highly desirable for their synthetic utility. Moreover, acid-promoted reactions would offer orthogonality to the previously described base-promoted reactions.

This study was driven by our long-standing interest[8] in organotrifluoroborate nucleophiles[9] due to their bench stability, low toxicity, and wide functional group tolerance. An underutilized feature of unsaturated organoboronates is their reaction as electron-rich π-nucleophiles with cationic intermediates via electrophilic deborylation (comparative to protodeborylation). We have been enabling new C−C bond-forming transformations from organoboronates in combination with a variety of electrophiles. Inspired by the above work, we envisioned that electrophilic oxyallyl cations generated from α-hydroxyl silyl enol ethers could be trapped by nucleophilic organoborates at the α-carbon with complete regioselectivity, affording unsaturated α,α′-substituted silyl enol ethers as masked ketones (Scheme 1, eq 5). The success of this strategy would provide a robust way for synthesizing ketones bearing unsaturated substituents at the α-positions.

Our investigation began with α-hydroxyl silyl enol ether **1a** reacting with 4-methoxyphenyl trifluoroborate (**2**). The success of this reaction critically depended on finding a catalyst that could ionize **1a** without negatively affecting the organotrifluoroborate. The performance of various Brønsted and Lewis acids was first examined. No significant conversion of enol ether **1a** to arylated adduct **3a** was observed when using Py·TfOH in CH_2Cl_2 at room temperature[7] (Table 1, entry 1). Theoretically, polar solvents would facilitate the formation of the charged oxyallyl cations. However, the replacement of CH_2Cl_2 with MeCN[7d] in the presence of Py·TfOH did not improve the reaction outcome (Table 1, entry 2). Other Brønsted acids such as TFAA, TfOH, or (+)-CSA also failed to afford a substantial amount of product **3a** (Table 1, entry 3). Encouragingly, the use of $(n\text{-Bu})_4NHSO_4$[8b] in MeCN provided **3a** in 41% yield. A screening of various Lewis acids was then carried out, and we observed the formation of enol **3a** in almost all cases.[10] The yield of **3a** increased to 65% when $Sc(OTf)_3$ (20 mol %) was employed (Table 1, entry 5). Notably, lithium salts gave higher yields and cleaner reactions (Table 1, entries 6−8), although they required a higher loading (0.5 equiv).[8e] Cationic lithium is a cheap, highly functional group-tolerant and benign reagent.[11] $LiPF_6$ appeared to be the most effective catalyst, as it afforded **3a** in 79% yield (Table 1, entry 8). It should be noted that the product **3a** was not observed in nonpolar solvents such as CH_2Cl_2 or PhMe, supporting the formation of a charged oxyallyl cation intermediate.

Table 1. Identifying Effective Reaction Conditions[a]

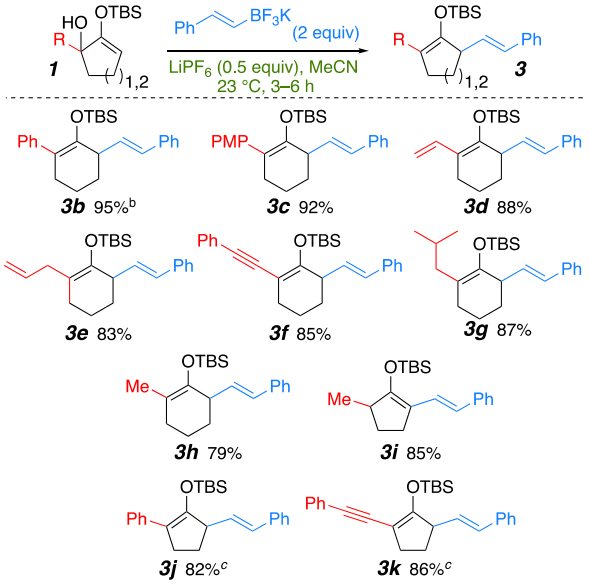


entry	catalyst	equiv	solvent	yield[b]
1	Py·TfOH	1	CH_2Cl_2	-
2	Py·TfOH	1	MeCN	-
3	Brønsted acids[c]	1	CH_2Cl_2	<10
4	$(n\text{-Bu})_4NHSO_4$	0.5	MeCN	41
5	$Sc(OTf)_3$	0.2	MeCN	65
6	LiOTf	0.5	MeCN	67
7	$LiClO_4$	0.5	MeCN	71
8	$LiPF_6$	0.5	MeCN	79[d]

[a]Reaction conditions: **1a** (0.2 mmol), 4-MeO-C_6H_4-BF_3K (0.4 mmol), and catalyst in solvent (2 mL) at room temperature (23 °C). [b]Via ^1H NMR peak integration relative to 4-nitrobenzoate. [c]Brønsted acids = TFAA, TfOH, and (+)-CSA. [d]Isolated in 78% yield.

With optimized conditions in hand, we then explored the substrate scope using a variety of α-hydroxyl silyl enol ethers. Various substituents at the α-carbon of the cyclic silyl enol ethers were incorporated for testing (Scheme 2). The results showed that the α-substituents did not significantly affect the reaction outcomes. The nucleophilic addition of organotrifluoroborates unsurprisingly occurred at the less substituted α′-carbon, providing the silyl enol ether products with complete regioselectivity and in high yield in every case (see **3b**−**k**). Substrates bearing aryl substituents afforded products **3b** and **3c** in >90% yield. More weakly activating substituents, such as vinyl or allyl groups, furnished adducts **3d** and **3e** in 88 and 83% yield, respectively. An alkynyl-substituted substrate gave product **3f** in 85% yield without any problems. Substrates with aliphatic α-substituents also afforded products **3g** and **3h** in good yield. Unfortunately, products from acyclic substrates or substrates without α-substituents have not yet been observed, indicating that the generated oxyallyl cations require resonance stabilization from π-donating groups, inductive stabilization from alkyl groups, or the rigidity of a ring system. We then turned our attention to five-membered ring substrates. The reactions proceeded at a high rate, providing **3i**−**k** within 5 min.

Scheme 2. Oxyallyl Cation Substitution Effects[a]



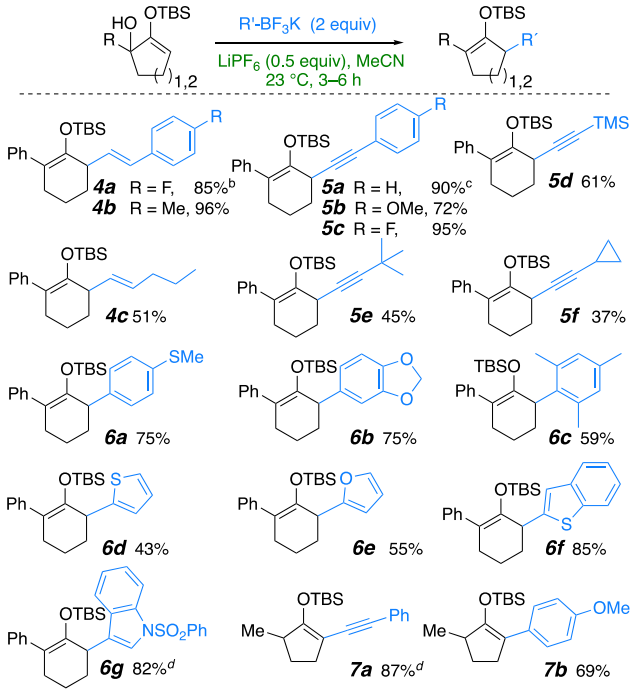
[a]Reaction conditions: **1** (0.2 mmol), styrenyltrifluoroborate (0.4 mmol), and $LiPF_6$ (0.5 equiv) in MeCN (2 mL) at room temperature. [b]Isolated in 82% yield when running on a 5.0 mmol scale. [c]Reaction completed in 5 min.

DOI: 10.1021/acs.orglett.9b02831
Org. Lett. 2019, 21, 7837−7840

Silyl enol ethers **3j,k** were obtained as expected. However, if the reaction forming **3j** was continued for more than 5 min, then a mixture of diastereomers was obtained due to olefin isomerization. The same phenomenon was seen in **3i**, where the conjugation to the added styrene results in only the isomerized product isolated. The greater facility for isomerization in the cyclopentane products is currently under investigation.[12]

Next, we examined a variety of trifluoroborate π-nucleophiles. A wide range of alkenyl-, alkynyl-, and aryl/heteroaryl trifluoroborates was found to perform well with these reaction conditions (Scheme 3). Styrenyl nucleophiles

Scheme 3. Scope of Organoborate π-Nucleophiles[a]



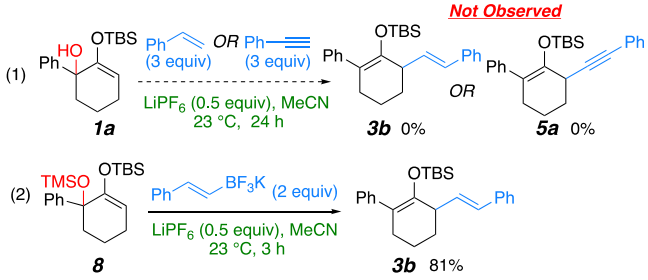
[a]Reactions were carried out with silyl enol ethers **1** (0.2 mmol), organotrifluoroborates (0.4 mmol), and $LiPF_6$ (0.5 equiv) in MeCN (2 mL) at room temperature. [b]Isolated in 82% yield when running on a 5.0 mmol scale. [c]Isolated in 83% yield when running on a 3.0 mmol scale. [d]Reaction completed in 5 min.

afforded products in excellent yield (**4a,b**). The addition of an electron withdrawing group at the para position in the phenyl ring did not significantly affect the reactivity. A less reactive nucleophile, such as pentenyl trifluoroborate, provided product **4c**, but in a lower yield. Although alkynyl boronates are often sensitive to acidic conditions, they were competent in the reaction to give alkynyl α-substituted silyl enol ethers (**5a–f**), which would be quite challenging to synthesize via other methods. Phenylethynyl trifluoroborate afforded **5a** in 90% yield. The use of a more electron-rich alkynyl borate surprisingly gave a lower yield (**5b**), assumingly due to an increased rate of product decomposition.[13] Ethynyltrimethylsilane trifluoroborate reacted to afford **5d** in 61% yield. The less reactive aliphatic alkynyl borates were also viable in the reaction to give **5e** and **5f** in useful yield. Aryl and heteroaryl borates were next tested. In general, $LiPF_6$ was able to promote the addition of electron-rich aromatic borates in moderate to high yield (**3a**, **6**, and **7**).

A methylthioether group was compatible with the reaction conditions, and **6a** was provided in 75% yield. A similar yield was obtained when using 3,4-(methylenedioxy)phenyl boronate (**6b**). The steric hindrance of the *o,o′*-disubstitution on mesitylene trifluoroborate was not a problem (**6c**). Sensitive heteroaryl borates like 2-thiophene and 2-furan afforded products **6d** and **6e** in acceptable yield,[14] whereas benzothiophene and protected indole nucleophiles gave products **6f** and **6g** in higher yield. Organoborate nucleophiles were also tested with cyclopentyl substrates. As was previously the case, alkenyl, alkynyl, and aryl borates were all reactive in good yield (**3i–k**, **7a,b**).

To gain insight into the hypothesized reaction mechanism, a control reaction between enol **1a** and styrene or phenylacetylene under the same conditions was run (Scheme 4, eq 1).

Scheme 4. Control Experiments



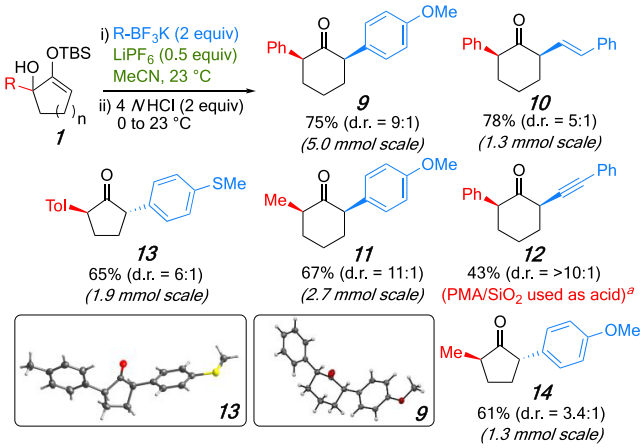
Neither product **3b** nor **5a** was observed, suggesting the essential activating role of the borate in the carbon nucleophiles. Furthermore, the replacement of the hydroxyl leaving group with a silyl ether in **8** did not significantly affect the reaction outcome, although we cannot exclude Li-promoted hydroxyl deprotection (Scheme 4, eq 2). This result favors an intermolecular addition of organoboronates to discrete oxyallyl cations rather than an intramolecular process via the coordination between the hydroxyl group and the nucleophile, followed by concerted C–C bond formation with C–O bond cleavage.[15] More detailed investigations into the mechanism of ionization to the oxyallyl cation and the C–C bond formation have been initiated.

To highlight the practicality and versatility of this strategy, reactions of **1** with several organoboronate nucleophiles were conducted on a larger scale (Scheme 5). A variety of highly useful transformations are available from silyl enol ethers.[16] To fulfill the primary purpose of this methodology, the substituted silyl enol ether products were converted to the corresponding ketones by adding 4 N HCl directly to the reaction mixtures. cis-Disubstituted ketones **9–12** (d.r. $\geq$ 5:1) were obtained as the major diastereomers from cyclohexanol substrates, whereas cyclopentenols provided trans-disubstituted ketones **13** (d.r. = 6:1) and **14** (d.r. = 3.4:1). Both ring sizes show thermodynamic control in the outcomes, and the stereochemical assignment was confirmed by crystal structures for **9** and **13**. To maintain the integrity of the alkyne, a solid-supported Brønsted acid was necessary. These results illustrate that diverse α,α'-disubstituted ketones can be efficiently synthesized by this method in a single step.

In conclusion, a general procedure for capturing oxyallyl cations by a wide range of alkenyl, alkynyl, and aryl/heteroaryl organotrifluoroborates via electrophilic deborylation was developed. This method afforded unsaturated α,α'-disubstituted silyl enol ethers as masked ketones in high yield with

DOI: 10.1021/acs.orglett.9b02831
Org. Lett. 2019, 21, 7837–7840

Scheme 5. One-Pot Synthesis of Disubstituted Ketones



[a]PMA/SiO_2 = phosphomolybdic acid supported on silica gel.[17]

complete regioselectivities. The silyl enol ether products can be easily transformed into the corresponding α,α'-disubstituted ketones in the same reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02831.

Complete experimental procedures and compound characterization data are provided (PDF)

Accession Codes

CCDC 1947177 and 1947185 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jmay@uh.edu.

ORCID

Jeremy A. May: 0000-0003-3319-0077

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Welch Foundation (grant E-1744) and the NSF (grant CHE-1800499) for generous financial support.

■ REFERENCES

(1) (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (b) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676. (c) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. *Chem. Soc. Rev.* **2015**, *44*, 7764.

(2) For reviews, see: (a) Harmata, M. *Chem. Commun.* **2010**, *46*, 8886. (b) Harmata, M. *Chem. Commun.* **2010**, *46*, 8904. For selected examples, see: (c) Fort, A. W. *J. Am. Chem. Soc.* **1962**, *84*, 4979. (d) Harmata, M.; Carter, K. W. *Tetrahedron Lett.* **1997**, *38*, 7985. (e) Krenske, E. H.; Houk, K. N.; Lohse, A. G.; Antoline, J. E.; Hsung, R. P. *Chem. Sci.* **2010**, *1*, 387. (f) Lohse, A. G.; Hsung, R. P. *Chem. - Eur. J.* **2011**, *17*, 3812. (g) Lo, B.; Lam, S.; Wong, W.-T.; Chiu, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 12120. (h) Lam, S. K.; Lam, S.; Wong, W.-T.; Chiu, P. *Chem. Commun.* **2014**, *50*, 1738. (i) Wu, Y.-K.; Dunbar, C. R.; McDonald, R.; Ferguson, M. J.; West, F. G. *J. Am. Chem. Soc.* **2014**, *136*, 14903. (j) LeFort, F. M.; Mishra, V.; Dexter, G. D.; Morgan, T. D. R.; Burnell, D. J. *J. Org. Chem.* **2015**, *80*, 5877. (k) Topinka, M.; Zawatzky, K.; Barnes, C. L.; Welch, C. J.; Harmata, M. *Org. Lett.* **2017**, *19*, 4106.

(3) For reviews, see: (a) Li, H.; Wu, J. *Synthesis* **2014**, *47*, 22. For selected examples, see: (b) Hardinger, S. A.; Bayne, C.; Kantorowski, E.; McClellan, R.; Larres, L.; Nuesse, M. *J. Org. Chem.* **1995**, *60*, 1104. (c) Mizuno, H.; Domon, K.; Masuya, K.; Tanino, K.; Kuwajima, I. *J. Org. Chem.* **1999**, *64*, 2648. (d) Krenske, E. H.; He, S.; Huang, J.; Du, Y.; Houk, K. N.; Hsung, R. P. *J. Am. Chem. Soc.* **2013**, *135*, 5242. (e) Li, H.; Hughes, R. P.; Wu, J. *J. Am. Chem. Soc.* **2014**, *136*, 6288.

(4) (a) Scadeng, O.; Ferguson, M. J.; West, F. G. *Org. Lett.* **2011**, *13*, 114. (b) Cordier, M.; Archambeau, A. *Org. Lett.* **2018**, *20*, 2265. (c) Hu, L.; Rombola, M.; Rawal, V. H. *Org. Lett.* **2018**, *20*, 5384.

(5) (a) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676. (b) Wu, Y.-K.; McDonald, R.; West, F. G. *Org. Lett.* **2011**, *13*, 3584. (c) Vaidya, T.; Eisenberg, R.; Frontier, A. J. *ChemCatChem* **2011**, *3*, 1531. (d) Basak, A. K.; Tius, M. A. *Org. Lett.* **2008**, *10*, 4073. (e) Marx, V. M.; Burnell, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 1685.

(6) (a) Tang, Q.; Chen, X.; Tiwari, B.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 1922. (b) Vander Wal, M. N.; Dilger, A. K.; MacMillan, D. W. C. *Chem. Sci.* **2013**, *4*, 3075. (c) Liu, C.; Oblak, E. Z.; Vander Wal, M. N.; Dilger, A. K.; Almstead, D. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 2134.

(7) (a) Ayala, C. E.; Dange, N. S.; Fronczek, F. R.; Kartika, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 4641. (b) Dange, N. S.; Stepherson, J. R.; Ayala, C. E.; Fronczek, F. R.; Kartika, R. *Chem. Sci.* **2015**, *6*, 6312. (c) Ayala, C. E.; Dange, N. S.; Stepherson, J. R.; Henry, J. L.; Fronczek, F. R.; Kartika, R. *Org. Lett.* **2016**, *18*, 1084. (d) Malone, J. A.; Cleveland, A. H.; Fronczek, F. R.; Kartika, R. *Org. Lett.* **2016**, *18*, 4408. (e) Stepherson, J. R.; Fronczek, F. R.; Kartika, R. *Chem. Commun.* **2016**, *52*, 2300.

(8) (a) Shih, J.-L.; Nguyen, T. S.; May, J. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 9931. (b) Nguyen, T. N.; Nguyen, T. S.; May, J. A. *Org. Lett.* **2016**, *18*, 3786. (c) Nguyen, T. N.; May, J. A. *Tetrahedron Lett.* **2017**, *58*, 1535. (d) Nguyen, T. N.; May, J. A. *Org. Lett.* **2018**, *20*, 112. (e) Nguyen, T. N.; May, J. A. *Org. Lett.* **2018**, *20*, 3618.

(9) (a) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275. (b) Molander, G. A. *J. Org. Chem.* **2015**, *80*, 7837.

(10) Please see the Supporting Information for a full list of experiments.

(11) (a) Karimi, B.; Maleki, J. *J. Org. Chem.* **2003**, *68*, 4951. (b) Kurono, N.; Yamaguchi, M.; Suzuki, K.; Ohkuma, T. *J. Org. Chem.* **2005**, *70*, 6530. (c) Malona, J. A.; Colbourne, J. M.; Frontier, A. J. *Org. Lett.* **2006**, *8*, 5661. (d) Sai, M.; Matsubara, S. *Synlett* **2014**, *25*, 2067.

(12) The working mechanistic hypothesis is that the addition to the allyl cation initially generates the isomer seen in the cyclohexene series.

(13) All of the alkyne products were prone to decomposition.

(14) These trifluoroboronates are highly prone to protodeboronation.

(15) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2004**, *45*, 729.

(16) For reviews, see: (a) Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181. (b) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.

(17) Kishore Kumar, G. D.; Baskaran, S. *J. Org. Chem.* **2005**, *70*, 4520.

DOI: 10.1021/acs.orglett.9b02831
Org. Lett. 2019, 21, 7837−7840