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Synthesis of *E*-Alkyl Alkenes from Terminal Alkynes via Ni-Catalyzed Cross-Coupling of Alkyl Halides with B-Alkenyl-9-borabicyclo[3.3.1]nonanes

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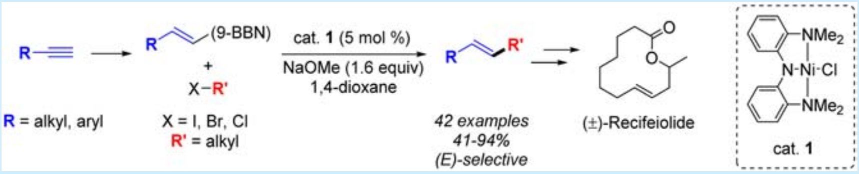
Supporting Information



ABSTRACT: The first Ni-catalyzed Suzuki−Miyaura coupling of alkyl halides with alkenyl-(9-BBN) reagents is reported. Both primary and secondary alkyl halides including alkyl chlorides can be coupled. The coupling method can be combined with hydroboration of terminal alkynes, allowing the expedited synthesis of functionalized alkyl alkenes from readily available alkynes with complete (*E*)-selectivity in one pot. The method was applied to the total synthesis of (±)-Recifeiolide, a natural macrolide.

Alkyl-substituted olefins are an important class of organic molecules, many of which exhibit interesting biological activity (Figure 1).[1] Cross-coupling reactions have become a major method for olefin synthesis.[2] However, the introduction of an alkyl group can be difficult, which is partially attributed to the tendency of metal alkyl intermediates to undergo unproductive *β*-H elimination.[3,4]

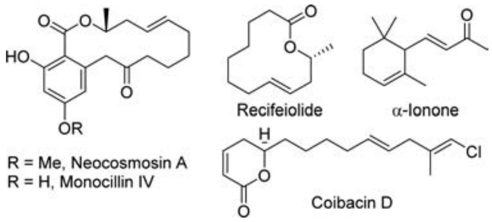
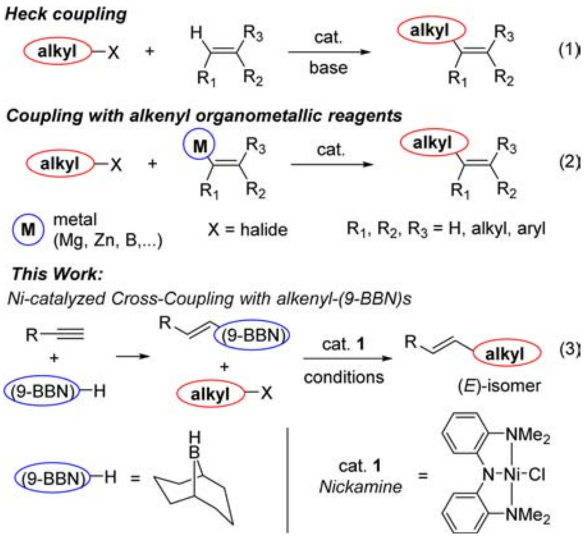


Figure 1. Selected complex molecules containing an alkyl (*E*)-alkene motif.

There are only a few protocols for alkyl Heck reactions, most of which are limited to intramolecular reactions (eq 1, Scheme 1).[5,6] As an alternative to alkyl Heck coupling, cross-coupling of alkyl halides with alkenyl organometallic reagents has been developed (eq 2, Scheme 1).[7,8] Due to its functional group compatibility and nontoxic nature, organoboron reagents are highly desirable partners for cross-coupling reactions.[9] While Suzuki reactions with alkenyl halides are well-known,[10] reports of Suzuki coupling between alkyl halides and alkenyl boron reagents are rare.[8] Despite the remarkable activity of Ni-based catalysts in cross-coupling of alkyl halides,[3] there are only two precedents of Ni-catalyzed alkyl−alkenyl Suzuki coupling. Fu and co-workers first reported the coupling of nonactivated alkyl iodides with alkenyl boronic acids.[11] More recently, Molander and co-workers developed Ni-catalyzed cross-coupling of alkyl bromides and iodides with potassium alkenyltrifluoroborates.[12]

Scheme 1. Different Types of Alkyl Alkenyl Cross-Coupling Reactions



To our knowledge, alkyl−alkenyl coupling using B-alkenyl-9-borabicyclo[3.3.1]nonanes (alkenyl-(9-BBN)) as coupling partners by nickel, or any other metal, has not been reported prior to this work. The advantage of alkenyl-(9-BBN) reagents relative to alkenyl boronic acids and potassium alkenyltri-

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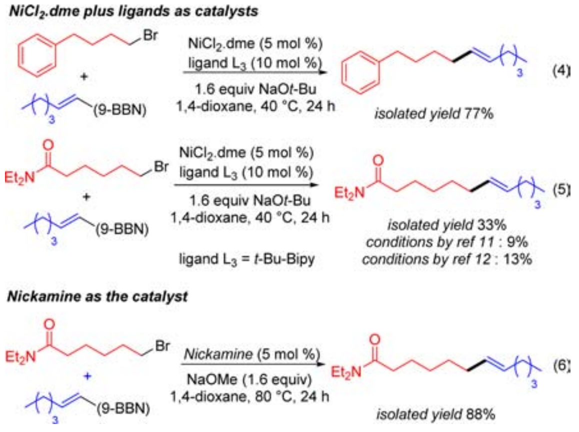
fluoroborates is that they can be prepared in one step by addition of (9-BBN)-H to alkynes.[13] The hydroboration is normally (*E*)-selective,[14] thus, only (*E*)-isomers of alkyl alkenes will be produced after cross-coupling. Here we report the first Ni-catalyzed cross-coupling of nonactivated alkyl halides with alkenyl-(9-BBN) reagents, which allows a *one-pot* synthesis of alkyl alkenes from terminal alkynes.

The coupling of 1-bromo-4-phenylbutane with (*E*)-9-(oct-1-en-1-yl)-(9-BBN) was used as the test reaction for the screening of the conditions. It was found that $NiCl_2$·dme together with 2,2′-bipyridine ligands could catalyze this reaction in good yields (Table S1). The optimized conditions are 5 mol % $NiCl_2$·dme, 10 mol % 4,4′-di-*tert*-butyl-2,2′-bipyridine (ligand L_3), 1.2 equiv of sodium *tert*-butoxide, 2 equiv of *tert*-amyl alcohol, 1,4-dioxane as solvent, and 40 °C as the reaction temperature (Scheme 2, eq 4). Under these conditions, the (*E*)-dec-5-en-1-ylbenzene was formed in 77% yield. The above reaction protocol was then applied for the coupling of functionalized alkyl halides. However, the yields were poor. For example, coupling of 6-bromo-*N*,*N*-diethylhexanamide with (*E*)-9-(oct-1-en-1-yl)-(9-BBN) had a yield of only 33% (Scheme 2, eq 5). Thus, the catalytic system comprising $NiCl_2$·dme and L_3 is not functional group tolerant. We hypothesized that the functional groups of the substrates poisoned the catalyst. To probe the active Ni species under these conditions, the reaction in eq 4 was conducted in the presence of 100 equiv of Hg (relative to the catalyst). The yield decreased from 77% to 16%, suggesting that heterogeneous Ni particles were responsible for the catalysis. Likely due to binding of the functional groups, this heterogeneous Ni catalyst loses its activity when functionalized substrates are used. The protocols of Fu[11] and Molander[12] were also applied for the coupling reaction in eq 5. However, low yields were again obtained (9% and 13%, respectively).

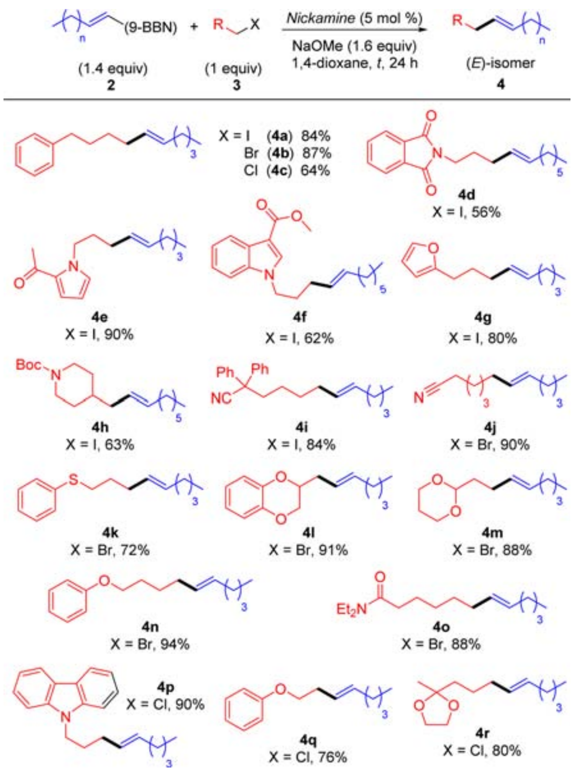
Scheme 2. Development of Nickel-Catalyzed Cross-Coupling of Alkyl Halides with Alkenyl-(9-BBN) Reagents



We reasoned that to develop functional-group-tolerant coupling of alkyl halides with alkenyl-(9-BBN) reagents, a robust Ni catalyst was required. Thus, we turned our attention to our previously developed catalyst, Nickamine ([(MeN_2N)-Ni−Cl], **1**. This catalyst is active for a large number of cross-coupling reactions of alkyl halides.[15] The catalyst is stable even when heated at more than 100 °C, and its strongly chelating pincer ligand should alleviate the binding of functional groups.[16] A slight modification of the conditions in Table S1 was necessary (Table S2). The modification includes using 1.6 equiv of sodium methoxide as the base and changing the temperature to 60 °C for alkyl iodides, 80 °C for alkyl bromides, and 100 °C for alkyl chlorides (Scheme 2, eq 6). The mechanism of this Suzuki−Miyaura coupling should be similar to analogous Kumada coupling catalyzed by Nickamine, which involves a radical-based bimetallic oxidative addition.[17] Thus, the difference in reaction temperature is consistent with the difference in carbon−halide bond dissociation energy.[18]

The optimized conditions using Nickamine as the catalyst were first applied for the coupling of alkenyl-(9-BBN) with functionalized primary alkyl halides (Scheme 3). Not only alkyl iodides (**4a**) and bromides (**4b**) but also alkyl chlorides (**4c**) could be coupled in good to excellent isolated yields. Only (*E*)-isomers of the olefins were obtained, which originated from the (*E*)-configuration of alkenyl-(9-BBN) reagents. When an alkenyl-(9-BBN) reagent with a (*Z*)-configuration was used, the corresponding (*Z*)-isomer of the olefin was obtained (Figures S4−S6, Supporting Information). The cross-coupling is therefore stereospecific. The coupling has high functional group tolerance. Amide (**4d**, **4o**), pyrrole (**4e**), ketone (**4e**) indole (**4f**), ester (**4f**), furan (**4g**), Boc-protected nitrogen (**4h**), nitrile (**4i**, **4j**), thioether (**4k**), dioxane (**4l**), acetal (**4m**, **4r**), ether (**4n**, **4q**), and carbazole (**4p**) groups are all compatible.

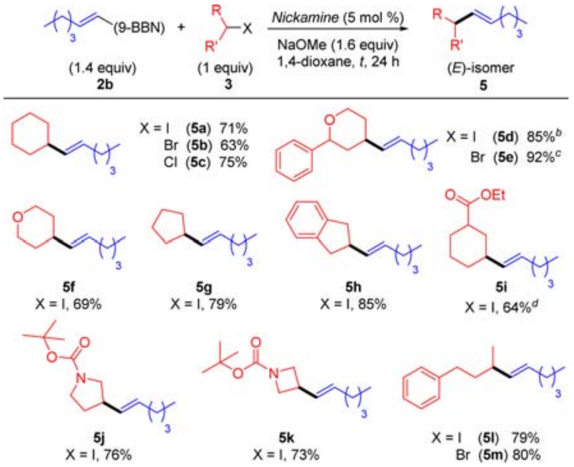
Scheme 3. Alkyl−Alkenyl Suzuki−Miyaura Cross-Coupling Reaction with Primary Alkyl Halides[a]



[a]Reaction conditions: **2** (1.4 equiv), **3** (0.5 mmol), Nickamine **1** (5 mol %), NaOMe (1.6 equiv), 1,4-dioxane (1 mL), 24 h, under N_2; for X = I, *t* = 60 °C; for X = Br, *t* = 80 °C; for X = Cl, *t* = 100 °C. Isolated yields are given, and the (*E*)-configuration was confirmed by ^1H NMR.

The scope of secondary alkyl halides was then explored using (*E*)-9-(hex-1-en-1-yl)-(9-BBN) as the cross-coupling partner (Scheme 4). Again good to excellent yields of (*E*)-olefins were obtained. Both cyclic and acyclic secondary alkyl halides could be coupled (**5a**, **5b**, **5c**, **5l**, **5m**). The yields for substrates

Scheme 4. Alkyl−Alkenyl Suzuki−Miyaura Cross-Coupling Reaction with Secondary Alkyl Halides[a]



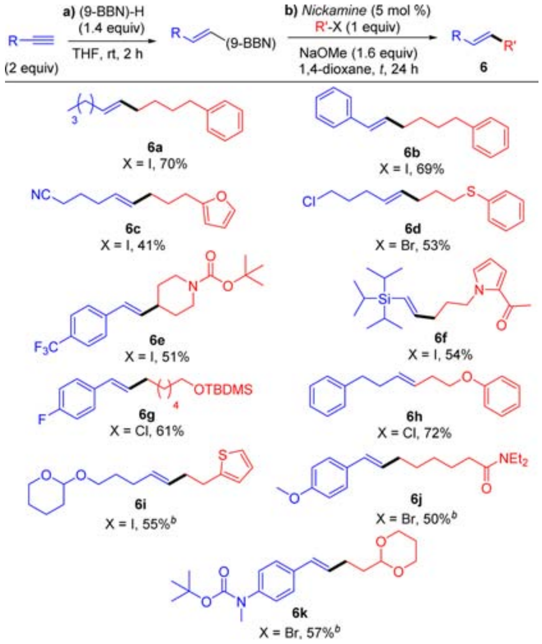
[a]Reaction conditions: **2b** (1.4 equiv), **3** (0.5 mmol), Nickamine **1** (5 mol %), NaOMe (1.6 equiv), 1,4-dioxane (1 mL), 24 h, under N_2; for X = I, *t* = 60 °C; for X = Br, *t* = 80 °C; for X = Cl, *t* = 100 °C. Isolated yields are given, and the (*E*)-configuration was confirmed by ^{1}H NMR. [b]*Cis*/*trans* ratio was 91:9, and both isomers were (*E*). [c]*Cis*/*trans* ratio was 90:10, and both isomers were (*E*). [d]*Cis*/*trans* ratio was 76:24, and both isomers were (*E*).

containing 4-, 5-, or 6-membered carbocycles are similar. Functional groups such as ester (**5i**), ether (**5d**, **5e**, **5f**), and N-Boc (**5j**, **5k**) were tolerated. The coupling is diastereoselective for substituted cyclohexyl and tetrahydro-2*H*-pyran halides (**5d**, **5e**, **5i**). The diastereomeric ratio (d.r.) of the coupling of **5d** and **5e** was about 90:10, while the d.r. for the coupling of **5i** was 76:24. This is consistent with the lower *A* value for ester (*A* = 1.2−1.3) than for the phenyl group (*A* = 2.8 on cyclohexane and even larger on tetrahydropyran).[19]

The one-pot synthesis of alkyl alkenes by sequential hydroboration of alkynes and Ni-catalyzed cross-coupling was next investigated (Scheme 5).[20] After the reaction of the (9-BBN)-H with the alkyne, THF was evaporated and the crude product was dissolved in 1 mL of 1,4-dioxane. This solution was added to a mixture containing appropriate amounts of Nickamine, NaOMe, and an alkyl halide. To our delight, the one-pot procedure was successful (Scheme 5). Both the alkyne and alkyl halide partners can be largely varied. Functional groups such as nitrile (**6c**), alkyl-Cl (**6d**), thioether (**6d**), CF_3 (**6e**), ketone (**6f**), silyl ether (**6g**), aryl-F (**6g**), benzylether (**6h**), amide (**6j**), acetal (**6i**, **6k**), and N-Boc (**6e**, **6k**) were tolerated on both coupling partners. As the alkyne partner can have an alkyl halide group (**6d**), the method can be potentially used for iterative coupling. Although the overall yields were lower than the corresponding cross-coupling reactions, considering that two steps were involved, the one-pot procedure was reasonably efficient. These results demonstrated the viability of synthesizing alkyl alkenes directly from the corresponding alkynes and using alkyl halides as electrophile partners.[21]

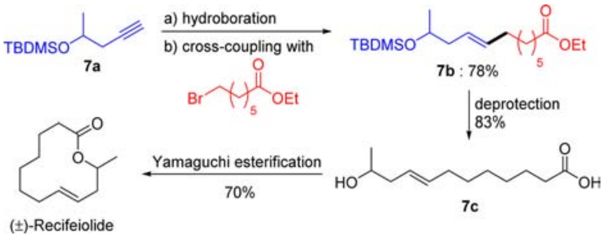
To further illustrate the utility of this method, the *one-pot* protocol was applied for the total synthesis of the (±)-Recifeiolide, a naturally occurring macrolide[22] (Scheme 6). This 12-membered lactone has been isolated as a metabolite of a fungus *Cephalosporium recifei*.[23] The reaction of the 4-pentyn-2-ol with TBDMS-Cl gave the corresponding protected alcohol **7a** in 77% yield. Compound **7a** was submitted to our one-pot conditions with the ethyl 7-bromoheptanoate to give the corresponding cross-coupling product **7b** with an isolated yield of 78% and complete (*E*)-stereochemistry. After deprotection, the product **7c** was obtained in 75% yield. Finally, the Yamaguchi esterification[24] of **7c** afforded the (±)-Recifeiolide in 70% yield. From commercially available reagents, the synthesis involves five steps with an overall yield of 35%. This is one of the most concise total synthesis of the (±)-Recifeiolide.[22]

Scheme 5. One-Pot Alkyl−Alkenyl Suzuki−Miyaura Cross-Coupling Reaction Starting from the Alkyne[a]



[a]Reaction conditions: **a)** Alkyne (2 equiv), (9-BBN)-H (1.4 equiv), THF (1 mL) at 0 °C then warmed to rt and stirred for 2 h before evaporation. **b)** (9-BBN)-compound (1.2 equiv), alkyl halide (0.5 mmol), *Nickamine* **1** (5 mol %), NaOMe (1.6 equiv), 1,4-dioxane (1 mL), 24 h, under N_2; for X = I, *t* = 60 °C; for X = Br, *t* = 80 °C; for X = Cl, *t* = 100 °C. Isolated yields are given and the (*E*)-configuration was confirmed by ^{1}H NMR. [b]For step **a)** reaction mixture was stirred at 0 °C for 2 h then at rt for 1 h before evaporation.

Scheme 6. Total Synthesis of the (±)-Recifeiolide



In summary, the first Ni-catalyzed cross-coupling of non-activated alkyl halides with alkenyl-(9-BBN) reagents is developed thanks to the activity and stability of Nickamine. The method provides a direct access to functionalized alkenes starting from readily available alkynes. The method has broad scope and high functional group tolerance. The synthetic utility of the method was demonstrated in the total synthesis of (±)-Recifeiolide.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02482.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Álvarez, R.; Vaz, B.; Gronemeyer, H.; de Lera, A. R. *Chem. Rev.* **2014**, *114*, 1−125. (b) Dachavaram, S. S.; Kalyankar, K. B.; Das, S. *Tetrahedron Lett.* **2014**, *55*, 5629−5631. (c) Wicklow, D. T.; Joshi, B. K.; Gamble, W. R.; Gloer, J. B.; Dowd, P. F. *Appl. Environ. Microbiol.* **1998**, *64*, 4482−4484. (d) Bovolenta, M.; Castronovo, F.; Vadalà, F.; Zanoni, G.; Vidari, G. *J. Org. Chem.* **2004**, *69*, 8959−8962.

(2) (a) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004. (b) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. *4*, Chapter 4.3. (c) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146−151. (d) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (e) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.

(3) For a recent review on Ni-catalyzed cross-coupling of nonactivated alkyl halides, see: Hu, X. L. *Chem. Sci.* **2011**, *2*, 1867−1886.

(4) (a) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674−688. (b) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656−2670. (c) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525−1532.

(5) For selected examples of an intermolecular alkyl Heck reaction, see: (a) Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2002**, *124*, 6514−6515. (b) Matsubara, R.; Gutierrez, A. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2011**, *133*, 19020−19023. (c) Liu, C.; Tang, S.; Liu, D.; Yuan, J.; Zheng, L.; Meng, L.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3638−3641. (d) Zou, Y.; Zhou, J. *Chem. Commun.* **2014**, *50*, 3725−3728. (e) McMahon, C. M.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 5974−5977.

(6) For selected examples of an intramolecular alkyl Heck reaction, see: (a) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340−11341. (b) Bloome, K. S.; McMahen, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 20146−20148. (c) Weiss, M. E.; Kreis, L. M.; Lauber, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11125−11128. (d) Harris, M. R.; Konev, M. O.; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 7825−7828. (e) Parasram, M.; Iaroshenko, V. O.; Gevorgyan, V. *J. Am. Chem. Soc.* **2014**, *136*, 17926−17929.

(7) For selected examples, see: for M = Mg: (a) Guérinot, A.; Reymond, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6521−6524. (b) Cahiez, G.; Duplais, C.; Moyeux, A. *Org. Lett.* **2007**, *9*, 3253−3254. For M = Si: (c) Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302−3303. For M = Zn: (d) Hatakeyama, T.; Nakagawa, N.; Nakamura, M. *Org. Lett.* **2009**, *11*, 4496−4499. (e) Choi, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 9102−9105. For examples of total synthesis using alkenyl nucleophiles, see: (f) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489.

(8) For examples with M = B, see: (a) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099−10100. (b) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662−13663. (c) Hashimoto, T.; Hatakeyama, T.; Nakamura, M. *J. Org. Chem.* **2012**, *77*, 1168−1173. (d) Yang, C.-T.; Zhang, Z.-Q.; Liu, Y.-C.; Liu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3904−3907.

(9) (a) Negishi, E-i. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E-i., de Meijere, A., Eds.; John Wiley & Sons, Inc.: New York, 2002; Vol. *2*, Chapter III. (b) Benderdour, M.; Bui-Van, T.; Dicko, A.; Belleville, F. *J. Trace Elem. Med. Biol.* **1998**, *12*, 2−7.

(10) (a) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Sato, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314−321. (b) Liron, F.; Fosse, C.; Pernolet, A.; Roulland, E. *J. Org. Chem.* **2007**, *72*, 2220−2223. For a review on Suzuki−Miyaura cross-coupling with alkenyl halides, see: (c) Doucet, H. *Eur. J. Org. Chem.* **2008**, *2008*, 2013−2030. For selected examples of total synthesis using Suzuki−Miyaura cross-coupling with alkenyl halides, see: (d) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073−10092. (e) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885−7892.

(11) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340−1341.

(12) Molander, G. A.; Argintaru, O. A. *Org. Lett.* **2014**, *16*, 1904−1907.

(13) (a) Brown, H. C.; Scouten, C. G.; Liotta, R. *J. Am. Chem. Soc.* **1979**, *101*, 96−99. (b) Colberg, J. C.; Rane, A.; Vaquer, J.; Soderquist, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 6065−6071.

(14) Miyaura, N.; Satoh, M.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 3745−3748.

(15) (a) Vechorkin, O.; Proust, V.; Hu, X. L. *J. Am. Chem. Soc.* **2009**, *131*, 9756−9766. (b) Vechorkin, O.; Godinat, A.; Scopelliti, R.; Hu, X. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 11777−11781. (c) Di Franco, T.; Boutin, N.; Hu, X. L. *Synthesis* **2013**, *45*, 2949−2958.

(16) Vechorkin, O.; Csok, Z.; Scopelliti, R.; Hu, X. L. *Chem. - Eur. J.* **2009**, *15*, 3889−3899.

(17) (a) Breitenfeld, J.; Ruiz, J.; Wodrich, M. D.; Hu, X. L. *J. Am. Chem. Soc.* **2013**, *135*, 12004−12012. (b) Breitenfeld, J.; Wodrich, M. D.; Hu, X. L. *Organometallics* **2014**, *33*, 5708−5715.

(18) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255−263.

(19) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2006.

(20) The term "one pot" is used rather than "cascade" because the reactions are conducted in the same reaction flask with sequential additions of reagents. For a discussion of "one-pot" reactions, see: Vaxelaire, C.; Winter, P.; Christmann, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3605−3607.

(21) For a recent example of Cu-catalyzed hydroalkylation of terminal alkynes, see: Uehling, M. R.; Suess, A. M.; Lalic, G. *J. Am. Chem. Soc.* **2015**, *137*, 1424−1427. However, this method only works for primary alkyl and benzyl triflates.

(22) (a) Boeckman, R. K., Jr.; Goldstein, S. W. The total synthesis of macrocyclic lactones. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1988; Vol. *7*, pp 1−139. For comparison, Corey performed the first total synthesis of the (±)-Recifeiolide in 8 steps and 52% overall yield. Mukaiyama realized this total synthesis in 8 steps and 12% overall yield. (b) Mochizuki, N.; Yamada, H.; Sugai, T.; Ohta, H. *Bioorg. Med. Chem.* **1993**, *1*, 71−75. The synthesis has 5 steps and a 35% overall yield

(23) Vesonder, R. F.; Stodola, F. H.; Wickerham, L. J.; Ellis, J. J.; Rohwedder, W. K. *Can. J. Chem.* **1971**, *49*, 2029−2032.

(24) Okuma, K.; Hirabayashi, S.-i.; Ono, M.; Shioji, K.; Matsuyama, H.; Bestmann, H. J. *Tetrahedron* **1998**, *54*, 4243−4250. The synthesis has 6 steps and a 40% overall yield.