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Copper-Promoted Coupling of Vinyl Boronates and Alcohols: A Mild Synthesis of Allyl Vinyl Ethers

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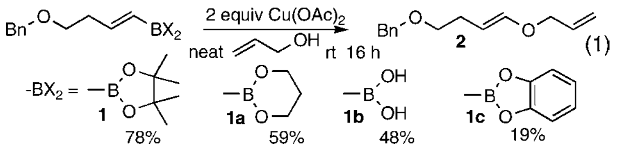
The vinyl ether is a deceptive functional group, as its simple structure belies the challenges inherent in its synthesis.[1] Because direct O-alkylation of enolates is not generally viable and vinylation of alcohols is limited to special cases, several types of indirect methods have been developed, including acid- or metal-catalyzed vinyl ether exchange;[2] addition/elimination on vinyl sulfoxides;[3] haloetherification followed by base elimination;[4] selenenyl etherification/selenoxide elimination;[5] catalyzed addition of alcohols to alkynes;[6] carbonyl alkenylation with phosphonium ylides, silyl anions, sulfone anions, or Tebbe reagents;[7] base- or metal-catalyzed isomerization;[8] and modification of existing vinyl ethers.[9] However, examination of the details of these processes reveals serious limitations, such as the need for strong bases, strong acids, toxic metals, or reactive electrophiles; limited substrate substitution; and lack of control over alkene stereochemistry.

The Claisen rearrangement[10] is an elegant example of the utility of allyl vinyl ethers in synthesis. The power of the Claisen rearrangement is derived from the formation of C−C bonds with control of stereochemistry through a chairlike transition state.[11] However, in contrast to derived reactions such as the Ireland ester enolate Claisen,[12] Carroll,[13] Eschenmoser,[14] and Johnson ortho ester[15] rearrangements, wherein the requisite substrates are readily prepared, the parent Claisen rearrangement is limited by challenges in preparing allyl vinyl ether substrates.

Therefore, there is an unmet need for a versatile, regiospecific, and stereospecific route to vinyl ether substrates that is compatible with acid- and base-sensitive groups, is easy to perform, uses inexpensive and nontoxic reagents, accommodates wide structural variability, and occurs with well-defined stereochemistry. Such a reaction may significantly expand the power of the Claisen rearrangement and promote greater utilization of vinyl ethers. This paper presents preliminary results toward such a process.

Chan and Lam[16] and separately Evans[17] developed copper-mediated aryl ether formation from aryl boronic acids and alcohols. These pioneering reports spurred numerous subsequent investigations into couplings of aryl and vinyl boronic acids with nitrogen and oxygen partners.[18] However, these protocols do not include simple alkyl or allyl vinyl ether targets. These methods are termed "modern Ullmann couplings", as they employ aryl or vinyl boronic acid substrates instead of aryl or vinyl halides.[19] Recent advances in the classic Ullmann reaction include a report by Buchwald on a copper-catalyzed synthesis of allyl vinyl ethers and their Claisen rearrangement products, but high-temperature conditions actually precluded isolation of the vinyl ethers.[20]

Our studies found that pinacol vinyl boronate esters couple with aliphatic alcohols using $Cu(OAc)_2$ at room temperature (rt) to provide vinyl ethers in good to excellent yields (eq 1): These results contrast with the modern Ullmann couplings as exemplified by the work of Chan and Lam on aryl ethers, wherein boronic acids were best.[16] We employed pinacol vinyl boronate esters derived from hydroboration of alkynes, but we also examined other boronate esters, boronic acids, boroxines, and boranes, which provided lower yields (eq 1). Thus, while others found boronic acids under dehydrating conditions favoring boroxine formation to be ideal in copper couplings, we found that pinacol esters were optimal for coupling with aliphatic alcohols. Another major difference is that our yields are based on 1 equiv of the vinyl boron partner, while the related work typically employs stoichiometric nucleophiles with excess boronic acid (2 equiv). Tests with different copper salts revealed that $Cu(OAc)_2$ is best, although several copper salts provided product. Addition of water is somewhat detrimental to the reaction, so anhydrous $Cu(OAc)_2$ is favored.[21]



Preliminary examples demonstrating functional group compatibility and coupling with aliphatic or allylic alcohols are illustrated in Table 1.[21] The coupling reaction is compatible with functional groups sensitive to acidic, basic, nucleophilic, oxidative, and radical conditions. The vinyl boronate ester substrates are readily prepared by hydroboration of alkynes using pinacol borane with or without transition-metal catalysts.[22] Neat alcohols were used, but a variety of solvents were compatible.[21]

Scheme 1. Mechanism of the Coupling Reaction

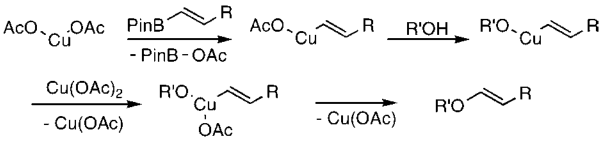
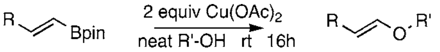
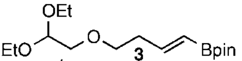
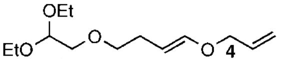
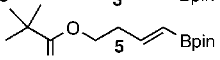
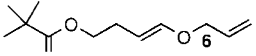
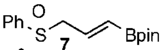
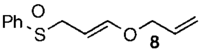
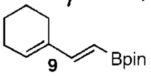
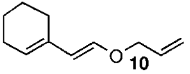
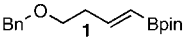
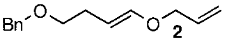
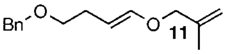
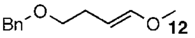
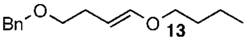


Table 1. Copper Coupling of Vinyl Boronates and Alcohols



(2)

Entry	Substrate	Product	Yield
1	 **3**	 **4**	72%
2	 **5**	 **6**	62%
3	 **7**	 **8**	51%
4	 **9**	 **10**	69%
5	 **1**	 **2**	78%
6	**1**	 **11**	61%
7	**1**	 **12**	64%
8	**1**	 **13**	52%

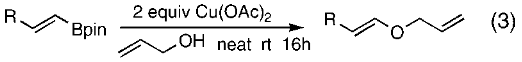
A modification of a working mechanism put forth by Evans[17b] and recently explored by Stahl[23] is illustrated in Scheme 1. Transmetalation and ligand exchange from $Cu(OAc)_2$ is followed by disproportionation and reductive elimination. The disproportionation step may explain the requirement for excess cupric acetate[21] and the absence of copper metal formation. Disproportionation may occur from an alkoxy vinyl copper

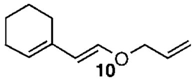
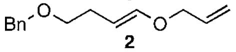
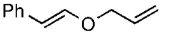
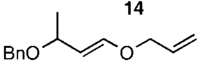
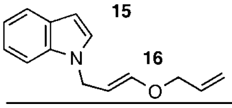
10.1021/ja907982w

rather than the acetoxy vinyl copper because of the greater ease of oxidation and the absence of vinyl acetate side products. This mechanism enables consideration of various reaction parameters.

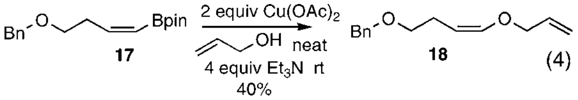
The reaction generates acetic acid when the alcohol coordinates to copper and possibly alcoholysis of acetoxy pinacol borate formed from transmetalation. A common side product observed in screening reactions was the alkene derived from protodeboration of the vinyl boronate ester. We postulated that addition of a tertiary amine might quench the acid without necessarily serving as a ligand for copper. This modification worked exceedingly well, and results for several substrates are shown in Table 2.

Table 2. Effect of Triethylamine on Copper-Promoted Coupling



Product	Yield w/o Et_3N	Yield w/ 4 equiv Et_3N
 **10**	69%	90%
 **2**	78%	99%
 **14**	39%	83%
 **15**	28%	99%
 **16**	69%	78%

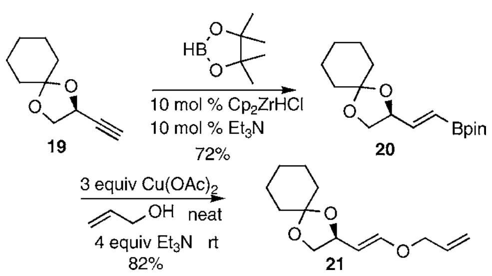
A significant issue in any coupling is stereospecificity. The reaction of boronate **17**, prepared via rhodium-catalyzed trans hydroboration,[24] under the optimized conditions led to a 40% yield of *Z* alkene **18** (eq 4):



While the yield was modest, the reaction was stereospecific, as no *E* alkene was detected.

Finally, the method was used for the synthesis of the exceptionally acid-labile target **21** (Scheme 2). Alkyne **19** was hydroborated using the Wang protocol[22a] to give **20**. Copper-promoted coupling with allyl alcohol in the presence of Et_3N at rt provided allyl vinyl ether **21** in 82% yield. For this sensitive target, the best yields were obtained with 3 equiv of cupric acetate.

Scheme 2



In conclusion, we have developed a mild, inexpensive, functional-group-tolerant, and stereospecific method for the synthesis of vinyl ethers that may have significant applications in organic synthesis. Subsequent reports will detail further modifications, ligand effects, and efforts toward a catalytic procedure.

Acknowledgment. We are grateful to the National Science Foundation and the Research Corporation for Science Advancement for financial support of this research.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Chiu, C. K.-F.; Berliner, M. A.; Li, Z. B. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Amsterdam, 2005; Vol. 2, pp 561−594. (b) Chiu, C. K.-F. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Elsevier Science Ltd.: Oxford, U.K., 1995; Vol. 2, pp 635−703.
(2) (a) Nakamura, A.; Tokunaga, M. *Tetrahedron Lett.* **2008**, *49*, 3729. (b) Bosch, M.; Schlaf, M. *J. Org. Chem.* **2003**, *68*, 5225. (c) Okimoto, Y.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2002**, *124*, 1590.
(3) (a) Yamamoto, T.; Fujita, S.; Sugawara, K.; Wantanabe, T. *Org. Prep. Proced. Int.* **1995**, *27*, 99. (b) Mandai, T.; Ueda, M.; Hasegawa, S.; Kawada, M. *Tetrahedron Lett.* **1990**, *31*, 4041.
(4) Park, H.; Kim, D.-H.; Yoo, M.-S.; Jew, S. *Tetrahedron Lett.* **2000**, *41*, 4579.
(5) Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 2286.
(6) (a) McDonald, F. E. *Strategies Tactics Org. Synth.* **2004**, *5*, 391. (b) Seo, S. Y.; Yu, X.; Marks, T. J. *J. Am. Chem. Soc.* **2009**, *131*, 263. (c) Ramana, C. V.; Mallik, R.; Gonnade, R. G.; Gurjar, M. K. *Tetrahedron Lett.* **2006**, *47*, 3649.
(7) (a) Ousset, J. B.; Mioskowski, C.; Yang, Y. L.; Falck, J. R. *Tetrahedron Lett.* **1984**, *25*, 5903. (b) Lakhrissi, M.; Chapleur, Y. *Angew. Chem., Int. Ed.* **1996**, *35*, 750. (c) Suprenant, S.; Chan, W. Y.; Berthelette, C. *Org. Lett.* **2003**, *5*, 4851. (d) Magnus, P.; Roy, G. *Organometallics* **1982**, *1*, 553. (e) Bourdon, B.; Corbet, M.; Fontaine, P.; Goekjian, P. G.; Gueyrard, D. *Tetrahedron Lett.* **2008**, *49*, 747. (f) Pine, S. H. *Org. React.* **1993**, *43*, 1.
(8) (a) Nelson, S. G.; Bungard, J. C.; Wang, K. *J. Am. Chem. Soc.* **2003**, *125*, 13000. (b) Higashino, T.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2000**, *2*, 4193. (c) Duval, E.; Zoltobroda, G.; Langlois, Y. *Tetrahedron Lett.* **2000**, *41*, 337.
(9) (a) Andersson, C. M.; Hallberg, A.; Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 3529. (b) Chandrasekhar, S.; Narsihmulu, C.; Sultana, S. S.; Reddy, N. R. *Org. Lett.* **2002**, *4*, 4399.
(10) (a) Majumdar, K. C.; Bhattacharyya, T.; Chattopadhyay, B.; Sinha, B. *Synthesis* **2009**, 2117. (b) Hiratani, K.; Albrecht, M. *Chem. Soc. Rev.* **2008**, *37*, 2413. (c) Tymoshenko, D. O. *Mini-Rev. Org. Chem.* **2008**, *5*, 85. (d) *The Claisen Rearrangement: Methods and Applications*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, Germany, 2007. (e) Majumdar, K. C.; Alam, S.; Chattopadhyay, B. *Tetrahedron* **2008**, *64*, 597. (f) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939.
(11) Vance, R. L.; Rondan, N. G.; Houk, K. N.; Jensen, F.; Borden, W. T.; Komornicki, A.; Wimmer, E. *J. Am. Chem. Soc.* **1988**, *110*, 2314.
(12) (a) McFarland, C. M.; McIntosh, M. C. In *The Claisen Rearrangement: Methods and Applications*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, Germany, 2007; pp 117−210. (b) Chai, Y.; Hong, S.-p.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905. (c) Reference 10f.
(13) (a) Hatcher, M. A.; Posner, G. H. In *The Claisen Rearrangement: Methods and Applications*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, Germany, 2007; pp 397−430. (b) Reference 10f.
(14) (a) Gradl, S. N.; Trauner, D. In *The Claisen Rearrangement: Methods and Applications*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, Germany, 2007; pp 367−396. (b) Reference 10f.
(15) (a) Langlois, Y. In *The Claisen Rearrangement: Methods and Applications*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, Germany, 2007; pp 301−366. (b) Reference 10f. (c) Ziegler, F. *Chem. Rev.* **1988**, *88*, 1423.
(16) (a) Lam, P. Y. S.; Bonne, D.; Vincent, G.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927. (b) Chan, D. M. T.; Monaco, K. L.; Li, R. H.; Bonne, D.; Clark, C. G.; Lam, P. Y. S. *Tetrahedron Lett.* **2003**, *44*, 3863. (c) Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933. (d) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941.
(17) (a) Decicco, C. P.; Song, Y.; Evans, D. A. *Org. Lett.* **2001**, *3*, 1029. (b) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937.
(18) (a) Chan, D. M. T.; Lam, P. Y. S. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 5. (b) Reference 19. (c) Batey, R. A.; Quach, T. D. *Org. Lett.* **2001**, *5*, 1381.
(19) (a) Monnier, F.; Taillefer, M. *Angew. Chem, Int. Ed.* **2009**, *48*, 2. (b) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (c) Nelson, T. D.; Crouch, R. D. *Org. React.* **2004**, *63*, 265. (d) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (e) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (f) Finet, J.-P.; Fedorov, A. Y.; Combes, S.; Boyer, G. *Curr. Org. Chem.* **2002**, *6*, 597.
(20) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978.
(21) See the Supporting Information for additional experimental results.
(22) (a) Wang, Y. D.; Kimball, G.; Prashad, A. S.; Wang, Y. *Tetrahedron Lett.* **2005**, *46*, 8777. (b) Pereira, S.; Srebnik, M. *Tetrahedron Lett.* **1996**, *37*, 3283. (c) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127. (d) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482.
(23) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044.
(24) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990.

JA907982W