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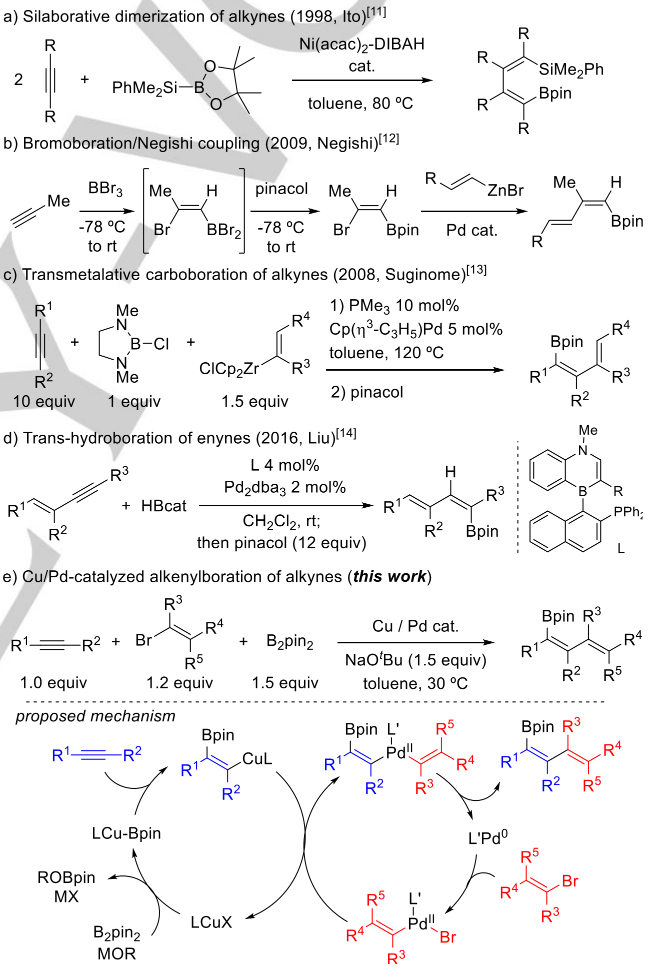
Stereoselective Synthesis of Borylated 1,3-Dienes by Synergistic Cu/Pd Catalysis

Nuria Vázquez-Galiñanes[a] and Martín Fañanás-Mastral*[a]

Abstract: A Cu/Pd-catalyzed alkenylboration of alkynes with alkenyl bromides and bis(pinacolato)diboron is reported. This transformation features the generation of a catalytic β-boryl-substituted C(sp^2)-Cu intermediate and subsequent Pd-catalyzed cross-coupling. The reaction tolerates a wide array of substrates and affords diversely substituted *syn*-borylated 1,3-dienes under mild conditions with total regio- and stereocontrol.

Boron-substituted 1,3-dienes represent an important class of compounds which serve as key building blocks in the synthesis of a wide range of bioactive natural products and organic materials.[1] The preparation of polyene frameworks by metal-catalyzed cross-coupling reactions[2] or Diels-Alder cycloadditions which render a versatile cyclic allyl-boron intermediate[3] illustrate the synthetic utility of these organoboron compounds. Notably, these transformations require the use of a stereodefined boron-substituted 1,3-diene to access structural unique molecular architectures. While most of the current strategies for the preparation of 1-boron-1,3-dienes give access to the isomer in which the boron atom is *anti* to the second alkene group,[4-10] methodologies that selectively afford the *syn* isomer are scarce and provide limited substitution patterns. A regio- and stereoselective Ni-catalyzed silaborative dimerization of alkynes was described by Ito and co-workers.[11] However, this procedure is non-selective for cross-dimerization of two different alkynes thus diminishing its versatility (Scheme 1a). As reported by Negishi, *syn*-borylated 1,3-dienes can also be accessed via alkyne *syn*-bromoboration and subsequent Pd-catalyzed cross-coupling with an alkenylzinc reagent.[12] This process requires conversion of the stereochemically unstable bromo-alkenyldibromoborane to the pinacolboronate which has to be isolated and purified prior to the cross-coupling, thus resulting into a multi-step methodology (Scheme 1b). Suginome and Daini reported a stereoselective method based on a Pd-catalyzed transmetalative carboboration of alkynes using air-sensitive chloroborane and alkenylzirconium reagents.[13] This transformation requires a large excess of the alkyne and the use of an organometallic compound under harsh conditions compromises the functional group tolerance (Scheme 1c). The *trans*-selective hydroboration of enynes represents an alternative to the use of organometallic reagents (Scheme 1d).[14] However, its reductive nature precludes the challenging formation of highly substituted 1,3-dienes.[15] Thus, a catalytic method which provides rapid and stereoselective access to diversely substituted *syn*-borylated 1,3-dienes from simple an abundant starting materials would be highly desirable.


a) Silaborative dimerization of alkynes (1998, Ito)[11]

b) Bromoboration/Negishi coupling (2009, Negishi)[12]

c) Transmetalative carboboration of alkynes (2008, Suginome)[13]

d) Trans-hydroboration of enynes (2016, Liu)[14]

e) Cu/Pd-catalyzed alkenylboration of alkynes (***this work***)

proposed mechanism

Scheme 1. Methodologies for the synthesis of *syn*-1-boron-1,3-dienes.

Cu-catalyzed carboboration of alkynes has become a powerful tool for their conversion into versatile alkenylboronates.[16] This transformation entails the catalytic formation of a nucleophilic β-boryl-substituted alkenylcopper intermediate and subsequent electrophilic trapping. So far, protocols involving alkyl,[17] aryl,[18] allyl,[19] alkynyl[20] and carbonyl[21] electrophiles have been described. The use of an alkenyl (pseudo)halide in this type of carboboration reaction might enable the *syn*-selective formation of 1-borylated 1,3-dienes; however, to the best of our knowledge, the Cu-catalyzed alkenylboration of alkynes has not been reported to date. Indeed, the use of this type of electrophiles

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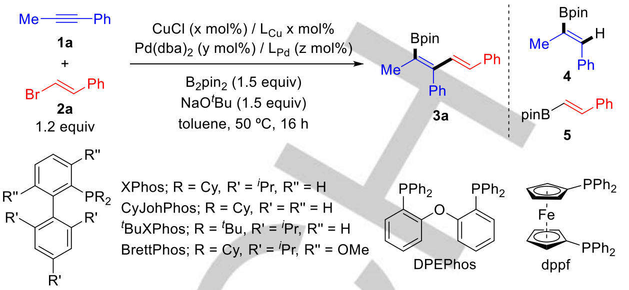
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate)) entails an additional challenge because there is potential for competitive migratory insertion of the LCu-Bpin intermediate across the alkenyl bromide.[22a] Based on previous work by our group[19b] and that of Semba/Nakao[18b,d] and Cazin[18c] on the use of synergistic Cu/Pd catalysis for the carboboration of alkynes,[22] we envisioned that a β-boryl alkenylcopper intermediate could be catalytically generated and exploited in a stereoretentive Pd-catalyzed cross-coupling with an alkenyl halide under cooperative catalysis regime (Scheme 1e). This approach features several advantages since 1) *syn*-selectivity would result from a *syn*-selective alkyne borylcupration; 2) alkynes are used as pro-nucleophiles thus avoiding the stoichiometric use of an alkenyl metal reagent; 3) activation of the alkenyl halide by the Pd co-catalyst would facilitate the coupling under mild conditions thus preventing competitive migratory insertion; 4) three different components would be assembled in a single operation thus providing high modularity to this transformation. Herein, we describe the successful implementation of this idea and thus the development of a catalytic process which allows for the regio- and stereoselective synthesis of diversely substituted *syn*-borylated 1,3-dienes from readily available B_2pin_2 and a wide variety of alkynes and alkenyl bromides.

We started our study by investigating the reaction between B_2pin_2, 1-phenyl-1-propyne (**1a**) and β-bromostyrene (**2a**) to evaluate the feasibility of the proposed transformation (Table 1 and Supporting Information). Initial experiment was carried out using PCy_3 as ligand for both catalysts. Although the desired *syn*-borylated 1,3-diene **3a** was the major product, considerable amounts of the protoboration product **4** and Miyaura borylation[23] product **5** were obtained (entry 1). A similar outcome was observed when using less basic and/or bidentate phosphines (entries 2 and 3). Testing several Pd co-catalysts, in-situ made from $Pd(dba)_2$ and different biarylphosphine ligands (entries 4-7; see also Supporting Information) and other Cu catalysts (entry 8), we found that the catalytic system comprising Pd/XPhos and Cu-PCy_3 enhanced the selectivity towards **3a**, representing an efficient catalyst for this transformation (entry 4). The use of a proper biarylphosphine is key to efficiently catalyze this transformation, since the use of more sterically demanding ligands such as BrettPhos did not lead to the formation of **3a** likely due to a non-efficient rate of transmetalation (entry 7). Importantly, both the Cu and Pd catalysts are necessary for this process. In the absence of Cu complex only Miyaura borylation product **5** was formed in trace amount (entry 9), while the reaction led to poor yield and selectivity under single Cu catalysis, even at higher temperatures (entry 10). Notably, catalyst loading could be reduced (Cu, 5 mol%; Pd, 2.5 mol%) providing diene **3a** in a slightly increased 87% yield (entry 11). We found that catalysts molar ratio is a key parameter for this transformation (entries 11-13), a 2:1 Cu:Pd ratio being the optimal one. This highlights the importance of matching the rates of both catalytic cycles to promote efficient catalysis. Finally, reaction temperature could be reduced to 30 ºC without erosion of yield (entry 14).

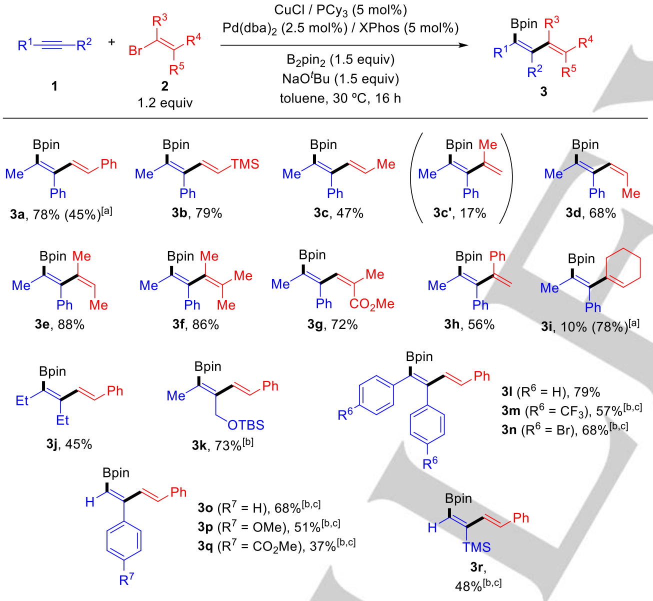
Table 1. Optimization studies



Entry [a]	L$_{Cu}$	L$_{Pd}$	x:y:z (mol%)	3a (%)[b]	4 (%)[b]	5 (%)[b]
1	PCy$_3$	PCy$_3$	10:5:10	50	25	5
2	PCy$_3$	DPEPhos	10:5:10	63	8	10
3	PCy$_3$	dppf	10:5:10	46	19	18
4	PCy$_3$	XPhos	10:5:10	80	12	-
5	PCy$_3$	CyJohnPhos	10:5:10	60	13	10
6	PCy$_3$	^{t}BuXPhos	10:5:10	40	36	-
7	PCy$_3$	BrettPhos	10:5:10	-	37	-
8	IMes	XPhos	10:5:10	70[c]	24	-
9	-	XPhos	0:5:10	-	-	6
10	PCy$_3$	-	10:0:0	13 (19)[d]	49 (50)[d]	- (13)[d]
11	PCy$_3$	XPhos	5:2.5:5	87	12	-
12	PCy$_3$	XPhos	5:5:5	48	20	-
13	PCy$_3$	XPhos	5:2.5:2.5	45	15	6
14[e]	PCy$_3$	XPhos	5:2.5:5	86 (78)[f]	10	-

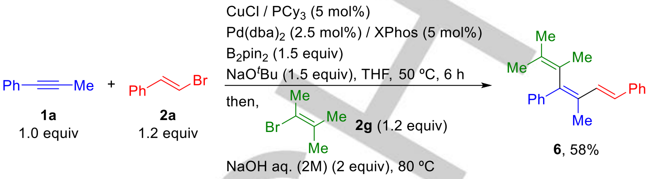
[a] Reactions run on a 0.5 mmol scale. [b] Determined by ^{1}H-NMR analysis using 1,3,5-trimethoxybenzene as internal standard. [c] 6% of α-borylated product was also obtained. [d] Results at 80 ºC shown in brackets. [e] Reaction run at 30 ºC. [f] Yield of isolated product shown in brackets.

Having a set of optimized conditions, we explored the scope of this transformation (Scheme 2). Different alkenyl bromides featuring all types of substitution pattern were used obtaining in all cases the corresponding borylated dienes **3a-h** with total chemo-, regio- and *syn*-stereoselectivity. Alkenyl triflates were also compatible substrates with this transformation. While acyclic triflates provided diminished yield, as illustrated in the synthesis of **3a**, 1-cyclohexenyl triflate proved to be much more efficient for the synthesis of product **3i** than the corresponding cyclic bromide. Importantly, the stereoretentive nature of this process preserves the stereochemical information of both the catalytically generated β-boryl alkenylcopper intermediate and the alkenyl bromide, thus providing stereomerically pure diene structures. Partial erosion of the alkenyl bromide structure was only observed when *trans*-1-bomo-1-propene **2c** was used. In this case diene **3c** was obtained together with a small amount of isomer **3c'** which probably results from coupling of in-situ formed 2-bromo-1-propene.[24] Noteworthy are the reactions with alkenyl bromides bearing functional groups such as trimethylsilyl and ester moieties that give stereoselective access to bifunctionalized dienes **3b** and **3g** which can serve as versatile linchpin reagents in the construction of polyene frameworks.[2] Regarding the alkyne partner, internal alkynes bearing both aromatic or aliphatic substituents proved to be very efficient substrates affording the corresponding products **3j-n** in good yields. Remarkably, in the case of **3n**, there was no evidence of borylation of the aryl bromide further highlighting the high chemoselectivity of this dual catalytic system. Terminal alkynes showed slightly diminished reactivity and required the use of a more elevated temperature (50 ºC) and higher catalyst loading. However, under these conditions dienes **3o-q** could be obtained in competitive yields. It is important to note that the use of trimethylsilylacetylene not only provides bifunctionalized diene **3r** but also opens the possibility to access less substituted borylated dienes by desilylation. Thus, 1-boron-1,3-dienes featuring all type of substitution patterns, ranging from simple 1,4-disubtituted structures to the challenging hexasubstituted systems which are difficult to access by other methods, are available by this novel Cu/Pd-catalyzed alkenylboration reaction.



Scheme 2. Scope of the Cu/Pd-catalyzed alkenylboration of alkynes. Yields refer to isolated products. [a] The corresponding alkenyl triflate was used. [b] At 50 ºC. [c] CuCl/PCy₃ (10 mol%), Pd(dba)₂ (5 mol%), XPhos (10 mol%).

An interesting feature of the present methodology is that the synthetic versatility of the boronic ester group can be exploited in combination with the initial catalyst to stereoselectively access triene structures in a one-pot alkenylboration/Suzuki coupling. This formal alkyne dialkenylation was illustrated by the synthesis of triene **6** in which the Pd complex acted as catalyst for both reactions (Scheme 3). Thus, treatment of alkyne **1a** with alkenyl bromide **2a** and B₂pin₂ under optimized conditions[25] and subsequent addition of alkenyl bromide **2g** and a NaOH aqueous solution led to triene **6** in 58% yield.



Scheme 3. Synthesis of triene **6** by one-pot alkenylboration/Suzuki coupling.

In summary, we have described a synergistic Cu/Pd-catalyzed three-component reaction of alkynes, B₂pin₂ and alkenyl bromides. The reaction tolerates a variety of substrates and affords diversely substituted *syn*-1-boron-1,3-dienes from good to excellent yields with a remarkable chemo-, regio- and stereoselectivity. Owing to the use of bench stable and readily available starting materials and the mild conditions, the method is practical and straightforward. Moreover, stereodefined conjugated trienes can also be accessed via a one-pot alkenylboration/Suzuki coupling in which the initial Pd complex acts as a two-fold catalyst.

Acknowledgements

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Keywords: boron • copper • dienes • palladium • synergistic catalysis

[1] J. Pyziak, J. Walkowiak, B. Marciniec, *Chem. Eur. J.* **2017**, *23*, 3502-3541.

[2] J. Cornil, A. Guérinot, J. Cossy, *Org. Biomol. Chem.* **2015**, *13*, 4129-4142.

[3] a) G. Hilt, P. Bolze, *Synthesis* **2005**, 2091-2115; b) B. B. Touré, D. G. Hall, *Chem. Rev.* **2009,** *109,* 4439-4486.

[4] Hydroboration of enynes: a) L. Garnier, B. Plunian, J. Mortier, M. Vaultier, *Tetrahedron Lett.* **1996**, *37*, 6699-6700; b) M. Tortosa, N. A. Yakelis, W. R. Roush, *J. Am. Chem. Soc.* **2008**, *130*, 2722-2723; Pd catalysis: c) Y. Matsumoto, M. Naito, T. Hayashi, *Organometallics* **1992**, *11*, 2732-2734; Zr catalysis: d) X. Gao, D. G. Hall, *Tetrahedron Lett.* **2003**, *44*, 2231-2235; Cu catalysis: e) Y. Sasaki, Y. Horita, C. Zhong, M. Sawamura, H. Ito, *Angew. Chem.* **2011**, *123*, 2830-2834; *Angew. Chem. Int. Ed.* **2011**, *50*, 2778-2782; Ag catalysis: f) H. Yoshida, I. Kageyuki, K. Takaki, *Org. Lett.* **2014**, *16*, 3512-3215.

[5] Borostannylation of enynes: R. R. Singidi, T. V. RajanBabu, *Org. Lett.* **2010**, *12*, 2622-2625.

[6] Cross-metathesis of vinylboronates with 1,3-butadienes: T. W. Funk, J. Efskind, R. H. Grubbs, *Org. Lett.* **2005**, *7*, 187-190; For a single example of *Z*-selective cross-metathesis, see: b) E. T. Kiesewetter, R. V. O'Brien, E. C. Yu, S. J. Meek, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2013**, *135*, 6026-6029.

[7] Heck coupling: a) A. P. Lightfoot, S. J. R. Twiddle, A. Whiting, *Org. Biomol. Chem.* **2005**, *3*, 3167-3172; b) J. J. Molloy, C. P. Seath, M. J. West, C. McLaughlin, N. J. Fazakerley, A. R. Kennedy, D. J. Nelson, A. J. B. Watson, *J. Am. Chem. Soc.* **2018**, *140*, 126-130.

[8] Negishi coupling: a) C. Mazal, M. Vaultier, *Tetrahedron Lett.* **1994**, *35*, 3089–3090; b) S. J. Lee, K. C. Gray, J. S. Paek, M. D. Burke, *J. Am. Chem. Soc.* **2008**, *130*, 466-468.

[9] Takai olefination: a) R. S. Coleman, M. C. Walczak, *Org. Lett.* **2005**, *7*, 2289–2291; b) R. S. Coleman, M. C. Walczak, E. L. Campbell, *J. Am. Chem. Soc.* **2005**, *127*, 16038–16039.

[10] As priority changes depending on the nature of the substituent at the carbon attached to boron, we use the *anti-syn* terminology instead of the *E-Z* notation to avoid misinterpretation.

[11] M. Suginome, T. Matsuda, Y. Ito, *Organometallics* **1998**, *17,* 5233-5235.

[12] C. Wang, T. Tobrman, Z. Xu, E. Negishi, *Org. Lett.* **2009**, *11*, 4092-4095.

[13] M. Daini, M. Suginome, *Chem. Commun.* **2008**, 5224-5226.

[14] S. Xu, Y. Zhang, B. Li, S.-Y. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 14566-14569.

[15] N. J. Green, A. C. Willis, M. S. Sherburn, *Angew. Chem.* **2016**, *128*, 9390-9394; *Angew. Chem. Int. Ed.* **2016**, *55*, 9244-9248.

[16] a) K. Semba, T. Fujihara, J. Terao, Y. Tsuji, *Tetrahedron*, **2015**, *71*, 2183-2197; b) H. Yoshida, *ACS Catal.* **2016**, *6*, 1799-1811; c) E. C. Neeve, S. J. Geier, I. A. I. Mkhalid, S. A. Westcott, T. B. Marder, *Chem. Rev.* **2016**, *116*, 9091-9161.

[17] a) R. Alfaro, A. Parra, J. Alemán, J. L. García Ruano, M. Tortosa, *J. Am. Chem. Soc.* **2012**, *134*, 15165-15168; b) H. Yoshida, I. Kageyuki, K. Takaki, *Org. Lett.* **2013**, 15, 952-955; c) K. Kubota, H. Iwamoto, E. Yamamoto, H. Ito, *Org. Lett.* **2015**, *17*, 620-623; d) W. Su, T.-J. Gong, Q. Zhang, Q. Zhang, B. Xiao, Y. Fu, *ACS Catal.* **2016**, *6*, 6417-6421; e) T. Itoh, Y. Shimizu, M. Kanai, *J. Am. Chem. Soc.* **2016**, *138*, 7528-7531.

[18] a) Y. Zhou, W. You, K. B. Smith, M. K. Brown, *Angew. Chem.* **2014**, *126*, 3543–3547; *Angew. Chem. Int. Ed.* **2014**, *53*, 3475-3479; b) K. Semba, Y. Nakao, *J. Am. Chem. Soc.* **2014**, *136*, 7567-7570; c) M. Lesieur, Y. D. Bidal, F. Lazreg, F. Nahra, C. S. J. Cazin, *ChemCatChem* **2015**, *7*, 2108-2112; d) K. Semba, M. Yoshizawa, Y. Ohtagaki, Y. Nakao, *Bull. Chem. Soc. Jpn.* **2017**, *90*, 1340–1343.

[19] a) H.-Y. Bin, X. Wei, J. Zi, Y.-J. Zuo, T.-C. Wang, C.-M. Zhong, *ACS Catal.* **2015**, *5*, 6670-6679; b) J. Mateos, E. Rivera-Chao, M. Fañanás-Mastral, *ACS Catal.* **2017**, *7*, 5340-5344; c) E. Rivera-Chao, M. Fañanás-Mastral, *Angew. Chem.* **2018**, *130*, 10093-10097; *Angew. Chem. Int. Ed.* **2018**, *57*, 9945-9949.

[20] J. T. Han, J. Yun, *Org. Lett.* **2018** *20*, 2104–2107.

[21] a) L. Zhang, J. Cheng, B. Carry, Z. Hou, *J. Am. Chem. Soc.* **2012**, *134*, 14314-14317; b) L.-J. Cheng, N. Mankad, *Angew. Chem.* **2018**, *130*, 10485-10489; *Angew. Chem. Int. Ed.* **2018**, *57*, 10328-10332.

[22] For a review, see: a) E. Rivera-Chao, L. Fra, M. Fañanás-Mastral, *Synthesis*, **2018**, 10.1055/s-0037-1610434. For Cu/Pd-catalyzed carboboration of alkenes, see: b) K. B. Smith, K. M. Logan, W. You, M. K. Brown, *Chem. Eur. J.* **2014**, *20*, 12032-12036; c) K. M. Logan, K. B. Smith, M. K. Brown, *Angew. Chem.* **2015**, *127*, 5317-5320; *Angew. Chem. Int. Ed.* **2015**, *54*, 5228-5231; d) T. Jia, P. Cao, B. Wang, Y. Lou, X. Yin, M. Wang, J. Liao, *J. Am. Chem. Soc.* **2015**, *137*, 13760-13763; e) K. M. Logan, M. K. Brown, *Angew. Chem.* **2017**, *129*, 869–873; *Angew. Chem. Int. Ed.* **2017**, *56*, 851-855. For Cu/Pd-catalyzed carboboration of 1,3-dienes, see: f) K. B. Smith, M. K. Brown, *J. Am. Chem. Soc.* **2017**, *139*, 7721-7724; g) S. R. Sardini, M. K. Brown, *J. Am. Chem. Soc.* **2017**, *139*, 9823-9826.

[23] J. Takagi, K. Takahashi, T. Ishiyama, N. Miyaura, *J. Am. Chem. Soc.* **2002**, *124*, 8001-8006.

[24] Although the mechanism of the isomerization is not entirely clear, it would most probably involve an addition-elimination process initiated by the insertion of **2c** into a B-metal bond. See ref. 23.

[25] Use of THF as solvent, which is perfectly compatible with the alkenylboration reaction, was necessary to achieve high efficiency in the Suzuki coupling.

Entry for the Table of Contents

Layout 2:

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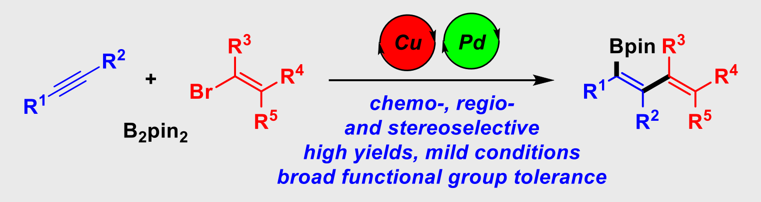

A Cu/Pd-catalyzed alkenylboration of alkynes with alkenyl bromides and bis(pinacolato)diboron is reported. This transformation features the synergistic generation of a catalytic C(sp^2)-Cu intermediate and subsequent Pd-catalyzed cross-coupling and affords diversely substituted *syn*-borylated 1,3-dienes with total regio- and stereocontrol.

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