CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201303683

Enantiospecific, Regioselective Cross-Coupling Reactions of Secondary Allylic Boronic Esters

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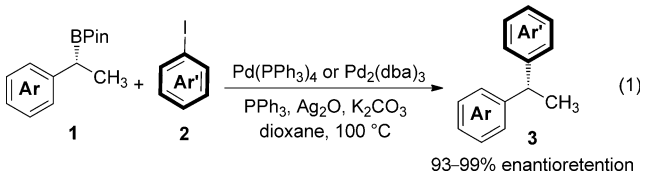
Dedicated to Professor Scott E. Denmark on the occasion of his 60th birthday

Asymmetric cross-coupling reactions in which stereochemistry-bearing C–C bonds are created are still in their infancy. Considering the wealth of compounds that can be prepared by cross-coupling methodologies, and the importance of synthetic methods leading to enantiomerically enriched products, this is a surprising reality. Advances in this area have occurred in the past few years, in the realm of enantioselective or enantiospecific cross-couplings of chiral electrophiles.[1]

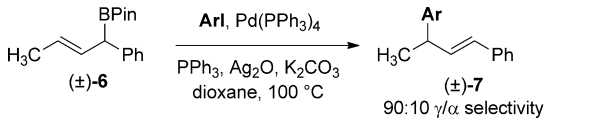
In the area of cross-coupling of stereodefined nucleophiles, Crudden originally reported the enantiospecific cross-coupling of chiral enantiomerically enriched benzylic boronic esters [Eq. (1)].[2,3]



(1)

Similar reaction conditions were shown by Aggarwal[4] to be applicable to tertiary propargylic boronic esters [Eq. (2)] and by Crudden to allylic boronates in racemic form [Eq. (3)].[5] Elegant examples of stereospecific cross-couplings of unrelated chiral organoboronic esters have followed from Suginome, Hall and Molander,[6] and recent advances have been reported in the stereospecific Stille cross-coupling reaction.[7,8]

(2)



(3)

Herein, we address the question of enantiospecificity, isomeric composition and mechanism in the coupling of enantiomerically enriched versions of allylic boronic esters, such as **6** and related derivatives. We demonstrate that the coupling proceeds with almost perfect stereoretention in all cases, and high γ-selectivity with several classes of substrates. The method provides a valuable addition to the cross-coupling of allylic organometallics, such as organosilanes,[9] in which the introduction of chirality in the starting materials can be challenging. Remarkably, this is the first report of the coupling of chiral, non-racemic allylic organoboron species,[10] a readily available class of substrates.[11]

After brief optimization, conditions for the cross-coupling of allylic boronic esters were found, with small but significant changes from the previously described coupling procedure[2] for benzylic boronic esters. Most importantly, with the addition of only two equivalents of PPh_3 relative to Pd, the reaction proceeded in high yield with virtually complete enantiospecificity.

In addition to providing good yields and high γ/α selectivities for substrates similar to those previously reported in racemic form,[5] equally good results were obtained regardless of the geometry of the olefin (entries 1 and 2, Table 1) and branched aliphatic substituents were well tolerated (entry 3, Table 1). Interestingly, although yields were lower, even trisubstituted allyl boronic esters were reactive (entry 4, Table 1). Entry 5 describes the only example in which there is an aromatic substituent on the vinyl group and this is the only example in which the cross-coupling proceeds with (albeit moderate) α-selectivity. The same propensity for styrene-containing substrates to react with α-selectivity was observed in previous work, and in these cases, se-

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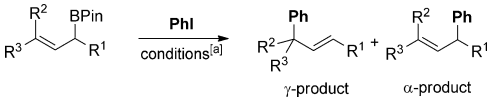
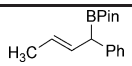
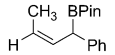
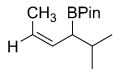
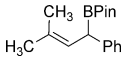
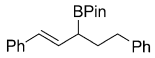
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201303683.

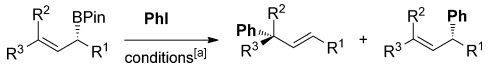
Table 1. Effect of substrate structure on regioselectivity of the cross-coupling reaction.[a]

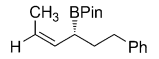
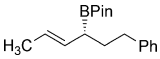
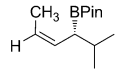
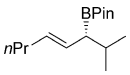
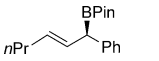


Entry	Compound		γ/α[b]	*E*/*Z*[c]	Yield [%][d]
1		(*E*)-**6**	97:3	99:1	65
2		(*Z*)-**6**	92:8	99:1	70
3		(*Z*)-**7**	91:9	99:1	77[e]
4		**8**	92:8	99:1	40
5		(*E*)-**9**	39:61	86:14	28[e]

[a] PhI (1 equiv), $Pd(dba)_2$ (5%), PPh_3 (10%), Ag_2O (1.5 equiv), DME (0.1 M), 90 °C, 16 h; [b] γ/α ratio determined by GC and/or ^{1}H NMR; [c] *E*/*Z* ratio for the major regioisomer; [d] isolated yield of major regioisomer unless otherwise stated; [e] isolated as mixture of regioisomers.

Table 2. Regio- and enantiospecificity in the Suzuki–Miyaura cross-coupling of enantiomerically enriched allylic boronic esters.[a]

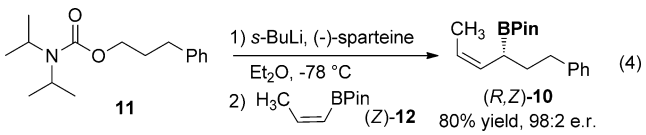


Compound		γ/α[b]	*E*/*Z*[b]	Yield [%][c]	e.r. (S.M.)[d]	e.s. [%][e]
	(*R*,*Z*)-**10**	83:17	94:6	75[f]	98:2	96
	(*R*,*E*)-**10**	94:6	78:22	81	98:2	100
	(*R*,*Z*)-**13**	90:10	99:1	77[f]	96:4	96
	(*R*,*E*)-**14**	92:8	99:1	71	96:4	100
	(*R*,*E*)-**15**	98:2	99:1	78	98:2	100

[a] See Table 1 footnote for conditions; [b] γ/α ratio determined by ^{1}H NMR, and *E*/*Z* selectivity is given for the major regioisomer; [c] Isolated yield of major isomer unless otherwise stated; [d] e.r. of the starting material; [e] enantiospecificity = *ee* product/*ee* starting material; [f] isolated as mixtures of γ and α products.

lectivities for α-arylation of 8:92 (*n*Bu in place of CH_2CH_2Ph) and 18:82 (*n*Hex in place of CH_2CH_2Ph) were observed.[5] The rationale for the α-selectivity in these cases is discussed in an overall mechanistic context below.

We next embarked on the synthesis of enantiomerically enriched versions of allylic boronic esters using Aggarwal lithiation-borylation methodology. For example, (*Z*)-**10** was prepared in 80% yield with a 98:2 e.r. [Eq. (4)].[11c,12]



Boronic esters (*E*)-**10**, (*E*)-**13**, and (*E*)-**14** were prepared in a similar manner in high yield and selectivity.[11c,12] However, the synthesis of (*E*)-**15**, which requires the lithiation and homologation of a benzylic carbamate, is significantly more challenging, as the lithiated derivative is configurationally unstable even at low temperature, leading to racemic products.[13]

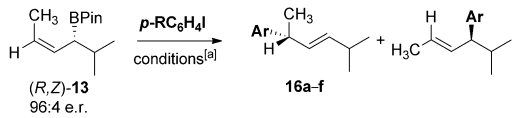
Hoppe has shown that under thermodynamic control, bisoxazoline ligands are effective with this class of carbamate, and we found that the combination of this ligand with the more reactive neopentyl glycol boronic ester provided the desired chiral allylic boronate (*R*,*E*)-**15** with 96% enantioselectivity.[14]

Having secured access to all of our key substrate classes in enantiomerically enriched form, we then examined the enantiospecificity of the coupling reaction. All of the substrate classes investigated reacted with virtually complete enantiospecificity (Table 2). The (*Z*)-allylic boronates **10** and **13** gave the γ-products with high *E* selectivity. In contrast, the (*E*)-allylic boronate **10** gave the γ-product with lower *E* selectivity, although high *E* selectivity was restored with the more hindered *i*Pr substituent. The *E*/*Z* selectivity is governed by $A^{1,3}$ strain between the R^1 and R^2 substituents in the conversion of A→B (Scheme 1).

Electronic effects with respect to the aryl halide were then explored in the cross-coupling of allylic boronic ester (*R*,*Z*)-**13** (96:4 e.r.). As shown in Table 3, electron-neutral or electron-rich aryl iodides gave the desired product in good yield and high isomeric purity favoring the (*E*)-γ-product (Table 3, entries 1–3). Electron poor aryl iodides resulted in decreased yields but still reacted with high enantiospecificities (Table 3, entries 4–6).

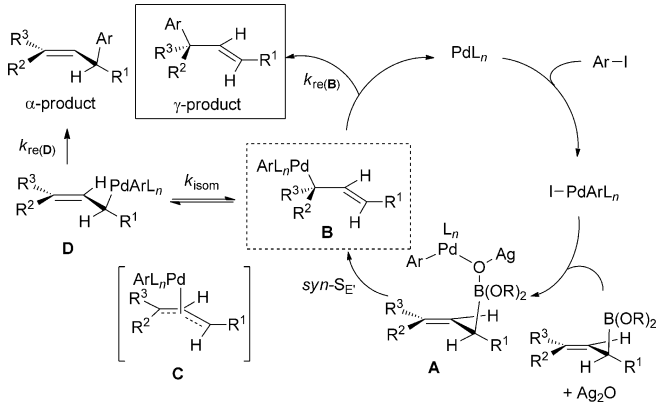
Similar to previous work with allyl silanes,[9] work by Yamamoto and Miyaura[10f] showed—consistent with our results with boronic esters—that the cross-coupling of racemic crotyl and methallyl trifluoroborates proceeds with S_E' re-

Table 3. Electronic effects in the Suzuki–Miyaura cross-coupling of aryl iodides with boronic ester (*R*,*Z*)-**13**.[a]



Entry	R	γ/α	*E*/*Z*[a]	Yield [%][b]	e.s. [%][c]
1	H	90:10	99:1	77	96
2	Me	91:9	99:1	72	93
3	OMe	85:15	99:1	72	96
4	$COCH_3$	90:10	99:1	60	96
5	Br	90:10	99:1	42	93
6	CF_3	91:9	99:1	42	93

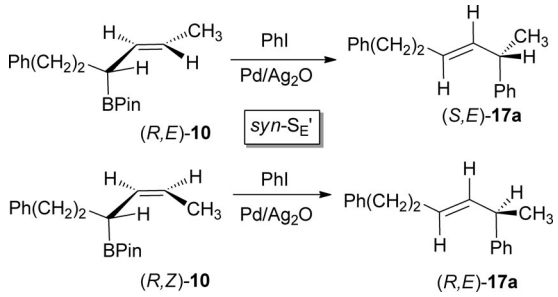
[a] See notes to Table 1; [b] isolated as mixture of γ and α products; [c] enantiospecificity, determined by chiral HPLC analysis, *ee* product/*ee* starting material.



Scheme 1. Mechanism for the formation of both the α- and γ-isomers.

giochemistry. Thus, it remained to be determined whether transmetalation occurred through *anti*- or *syn*-S_E' type reactions, which would lead to opposite stereoisomers of the product.[9] Mechanistic studies on the Suzuki–Miyaura reaction[15] point to likely pathways that involve a B–O–Pd linkage (**A**, Scheme 1) prior to transmetalation, such that the *syn*-S_E' intramolecular transmetalation would be predicted. This leads ultimately to organopalladium intermediate **B**, which subsequently undergoes reductive elimination generating the γ product.

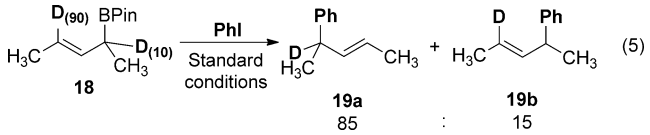
In order to test this hypothesis, the absolute stereochemistry of the products was determined and was found to correlate with olefin stereochemistry.[16] Thus, (*R*,*E*)-**10** was shown to give (*S*,*E*)-**17a**, whereas cross-coupling of the geometrical isomer (*R*,*Z*)-**10** gave (*R*,*E*)-**17a** (Scheme 2). This is consistent with *syn*-S_E' transmetalation.



Scheme 2. Absolute configuration of products and the relationship to mechanism of transmetalation.

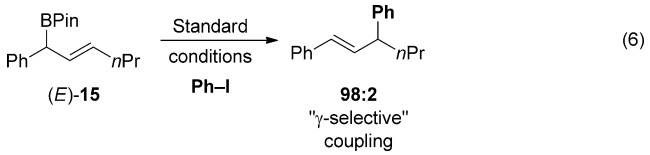
The involvement of π-allyl intermediates in the transformation was considered next.[17] Isomerization of the σ-bonded transmetalated intermediate **B** to the isomeric organopalladium intermediate **D**, could occur prior to reductive elimination. If this isomerization occurred fully, the ratio of γ/α cross-coupled products would be solely dependent on the relative rates of reductive elimination from intermediates **B** or **D** (Scheme 1).

To test the involvement of π-allyl intermediate **C**, we prepared a selectively deuterated allylic boronic ester, **18**, in which the steric and electronic effects of the two substituents are equivalent. Subjecting **18** (90:10 mixture of γ/α D-isomers) to our standard conditions gave an 85:15 (±5%) ratio in favor of γ product **19a**, indicating that reductive elimination is faster than isomerization via π-allyl intermediate **C** [Eq. (5)]. Indeed, it appears that on the order of 95% of the transmetalated intermediate **A** proceeds to product without isomerization through **C**.

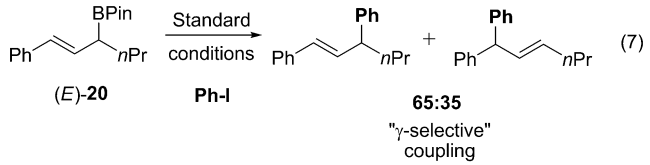


(5)

The synthesis of a deuterated diphenyl substituted version of **18** was not possible due to facile borotropic shifts, making a conclusive statement on the mechanism of the reaction of diaryl substrates difficult. However, it was observed that starting materials in which one aryl group is present on either end of the allylic unit, that is, (*E*)-**15** or (*E*)-**20**,[18] give the same major isomer [Eqs. (6), (7)], which does suggest a more significant role of π-allyl intermediates.[19]



(6)



(7)

Interestingly, however, the selectivity of the cross-coupling starting from (*E*)-**20** is markedly lower than that starting from (*E*)-**15**. In the latter case, the high selectivity can be explained if the reaction proceeds through the expected S_E'-transmetalation yielding organopalladium intermediate **B**, in which the olefin and aromatic ring are in conjugation (R^1 = Ph). Direct reductive elimination ($k_{re(B)}$) then gives the γ product in high selectivity, as observed with fully aliphatic systems.[20] For (*E*)-**20**, S_E'-transmetalation disrupts conjugation, forming intermediate **B** in which R^3 = Ph. Isomerization of this intermediate to **D** (via **C**) followed by reductive elimination $k_{re(D)}$ appears to be preferred, presumably driven by the conjugated styrene unit. The low selectivity observed suggests that reductive elimination from **B** still occurs to some extent, either directly from **B**, or after isomerization to **C**.[21]

In conclusion, we have described the first enantioselective Suzuki–Miyaura cross-coupling of chiral, enantioenriched secondary allylic boronic esters. The reaction proceeds with high γ-regioselectivity and high retention of chirality. Mechanistic studies show that the reactions proceed via γ-selective transmetalation followed by reductive elimination; the

latter process competes with isomerization to the π-allyl intermediate. Deuterium labeling studies show that direct reductive elimination is faster than formation of π-allyl intermediates for alkyl substituted allylic boronates. In addition to the synthetic utility of this transformation, the reaction provides the first independent confirmation that the transmetalation of boronic esters proceeds via a *syn* pathway, in accord with mechanistic studies that show the importance of the B–O–Pd linkage for facile transmetalation.

Experimental Section

General procedure for cross-coupling reactions of secondary allylic boronic esters: In a nitrogen-atmosphere glovebox, aryl iodide (1.0 equiv), secondary allylic boronic ester (1.2 equiv), Ag_2O (1.5 equiv), $Pd(dba)_2$ (0.05 equiv), and PPh_3 (0.1 equiv) were added to a 1 dram vial and taken up in DME (0.1 M). The reaction solution was sealed in the glovebox, removed, and heated to 90 °C in an oil bath for 18 h. Once cooled, the reaction solution was passed through a silica plug and washed with copious amounts of EtOAc then the solvents were removed under reduced pressure with a rotary evaporator. GC or ^{1}H NMR analysis was used to determine γ/α and *E*/*Z* ratio of products. The crude mixture was purified by silica gel chromatography to obtain desired product. Detailed procedures for the individual substrates are provided in the Supporting Information.

Acknowledgements

C.M.C. acknowledges the Natural Sciences and Engineering Research Council (NSERC) for support of this work in terms of a discovery grant, an accelerator grant and a research tools grant. WPI-ITbM is acknowledged for support of this work. The Canada Foundation for Innovation (CFI) is acknowledged for a Leader's Opportunity Fund to C.M.C. V.K.A. thanks the Swiss National Foundation for a fellowship (LCB), and the European Research Council (ERC grant no. 246785) for financial support.

Keywords: allylboronate · cross-coupling · stereospecificity · Suzuki–Miyaura · synthetic methods

[1] a) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417–1492; b) J. T. Binder, C. J. Cordier, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 17003–17006; c) Z. Lu, G. C. Fu, *Angew. Chem.* **2010**, *122*, 6826–6828; *Angew. Chem. Int. Ed.* **2010**, *49*, 6676–6678; d) B. W. Glasspoole, C. M. Crudden, *Nat. Chem.* **2011**, *3*, 912–913; e) M. R. Harris, L. E. Hanna, M. A. Greene, C. E. Moore, E. R. Jarvo, *J. Am. Chem. Soc.* **2013**, *135*, 3303–3306; f) B. L. Taylor, M. R. Harris, E. R. Jarvo, *Angew. Chem.* **2012**, *124*, 7910–7913; *Angew. Chem. Int. Ed.* **2012**, *51*, 7790–7793; g) B. L. H. Taylor, E. C. Swift, J. D. Waetzig, E. R. Jarvo, *J. Am. Chem. Soc.* **2011**, *133*, 389–391; h) Q. Zhou, H. D. Srinivas, S. Dasgupta, M. P. Watson, *J. Am. Chem. Soc.* **2013**, *135*, 3307–3310; i) P. Maity, D. M. Shacklady-McAtee, G. P. A. Yap, E. R. Sirianni, M. P. Watson, *J. Am. Chem. Soc.* **2013**, *135*, 280–285; j) A. López-Pérez, J. Adrio, J. C. Carretero, *Org. Lett.* **2009**, *11*, 5514–5517; k) M.-B. Li, X.-L. Tang, S.-K. Tian, *Adv. Synth. Catal.* **2011**, *353*, 1980.

[2] D. Imao, B. W. Glasspoole, V. S. Laberge, C. M. Crudden, *J. Am. Chem. Soc.* **2009**, *131*, 5024–5025.

[3] B. W. Glasspoole, M. S. Oderinde, B. D. Moore, A. Antoft-Finch, C. M. Crudden, *Synthesis* **2013**, 1759–1763.

[4] B. M. Partridge, L. Chausset-Boissarie, M. Burns, A. P. Pulis, V. K. Aggarwal, *Angew. Chem.* **2012**, *124*, 11965–11969; *Angew. Chem. Int. Ed.* **2012**, *51*, 11795–11799.

[5] B. W. Glasspoole, K. Ghozati, J. Moir, C. M. Crudden, *Chem. Commun.* **2012**, *48*, 1230–1232.

[6] a) T. Awano, T. Ohmura, M. Suginome, *J. Am. Chem. Soc.* **2011**, *133*, 20738–20741; b) T. Ohmura, T. Awano, M. Suginome, *J. Am. Chem. Soc.* **2010**, *132*, 13191–13193; c) G. A. Molander, S. R. Wisniewski, *J. Am. Chem. Soc.* **2012**, *134*, 16856–16868; d) D. L. Sandrock, L. Jean-Gerard, C.-Y. Chen, S. D. Dreher, G. A. Molander, *J. Am. Chem. Soc.* **2010**, *132*, 17108–17110; e) J. C. H. Lee, R. MacDonald, D. G. Hall, *Nat. Chem.* **2011**, *3*, 894–899.

[7] L. Li, C.-Y. Wang, R. Huang, M. R. Biscoe, *Nat. Chem.* **2013**, *5*, 607–612.

[8] a) M. Goli, A. He, J. R. Falck, *Org. Lett.* **2011**, *13*, 344–346; b) R. Kalkofen, H. Dieter, *Synlett* **2006**, 1959–1961.

[9] a) S. E. Denmark, N. S. Werner, *Org. Lett.* **2011**, *13*, 4596–4599; b) S. E. Denmark, N. S. Werner, *J. Am. Chem. Soc.* **2010**, *132*, 3612–3620; c) S. E. Denmark, N. S. Werner, *J. Am. Chem. Soc.* **2008**, *130*, 16382–16393; d) Y. Hatanaka, K.-I. Goda, T. Hiyama, *Tetrahedron Lett.* **1994**, *35*, 1279–1282; e) S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2007**, *129*, 12650–12651.

[10] For coupling reactions of achiral allylic organoboron species, see: a) H. Doucet, *Eur. J. Org. Chem.* **2008**, 2013–2030; b) A. S. Fürstner, G. Seidel, *Synlett* **1998**, 161–162; c) E. G. T. Occhiato, A. Guarna, *J. Org. Chem.* **2001**, *66*, 2459–2465; d) S. Kotha, M. Behera, V. R. Shah, *Synlett* **2005**, 1877–1880; e) P. Zhang, L. A. Brozek, J. P. Morken, *J. Am. Chem. Soc.* **2010**, *132*, 10686–10688; f) Y. Yamamoto, S. Takada, N. Miyaura, T. Iyama, H. Tachikawa, *Organometallics* **2009**, *28*, 152–160; g) E. F. Flegeau, U. Schneider, S. Kobayashi, *Chem. Eur. J.* **2009**, *15*, 12247–12254; h) S. Sebelius, V. J. Olsson, O. A. Wallner, K. J. Szabo, *J. Am. Chem. Soc.* **2006**, *128*, 8150–8151; i) Y. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **2013**, *135*, 10642–10645.

[11] a) D. S. Matteson, *Tetrahedron* **1998**, *54*, 10555–10606; b) H. Ito, C. Kawakami, M. Sawamura, *J. Am. Chem. Soc.* **2005**, *127*, 16034–16035; c) V. K. Aggarwal, M. Althaus, A. Mahmood, J. R. Suarez, S. P. Thomas, *J. Am. Chem. Soc.* **2010**, *132*, 4025–4028.

[12] J. L. Stymiest, G. Dutheuil, A. Mahmood, V. K. Aggarwal, *Angew. Chem.* **2007**, *119*, 7635–7638; *Angew. Chem. Int. Ed.* **2007**, *46*, 7491–7494.

[13] D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376–2410; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282–2316.

[14] H. Lange, R. Huenerbein, R. Frohlich, S. Grimme, D. Hoppe, *Chem. Asian J.* **2008**, *3*, 78–87.

[15] a) K. Matos, J. A. Soderquist, *J. Org. Chem.* **1998**, *63*, 461–470; b) C. Amatore, A. Jutand, G. Le Duc, *Chem. Eur. J.* **2011**, *17*, 2492–2503; c) B. P. Carrow, J. F. Hartwig, *J. Am. Chem. Soc.* **2011**, *133*, 2116–2119; d) A. J. J. Lennox, G. Lloyd-Jones, *Angew. Chem.* **2013**, *125*, 7506–7515; *Angew. Chem. Int. Ed.* **2013**, *52*, 7362–7370.

[16] Note that this was accomplished by RuO_4 oxidation. See the Supporting Information for details.

[17] a) U. Kazmaier, *Topics in Organic Chemistry 38: Transition Metal Catalysed Enantioselective Allylic Substitution in Organic Synthesis*, Springer, Berlin, **2012**; Szabo proposes an alternative mechanism for highly γ-selective arylations of allylic boronic esters, which involves carbopalladation followed by subsequent elimination of the palladium boronate (see ref. [10h]). The stereospecificity observed here is inconsistent with such a mechanism in our system.

[18] Derivatives of **20** in which the alkyl group are *n*Bu and *n*Hex also give α-selective couplings; see ref. [5].

[19] Borotropic shifts were not observed for these compounds.

[20] The presence of the conjugated styrene unit may even magnify $k_{re(B)}$ versus k_{isom}.

[21] It is also possible that the styrene unit in **20** somehow promotes α-selective transmetalation.

Received: September 19, 2013
Published online: December 2, 2013

