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Stereoselective Synthesis of (*E*)-(Trisubstituted alkenyl)borinic Esters: Stereochemistry Reversed by Ligand in the Palladium-Catalyzed Reaction of Alkynylborates with Aryl Halides

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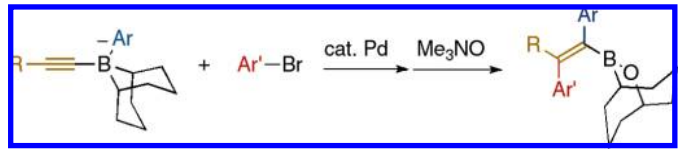
ABSTRACT



The palladium-catalyzed reaction of alkynylborates with aryl halides stereoselectively gave (*E*)-(trisubstituted alkenyl)-9-BBNs, in which two different aryl groups were installed *trans* to each other.

Organoboron compounds are stable and easily handled organometallics with well understood reactivities, rendering them indispensable synthetic reagents for carbon−carbon bond formation.[1] In addition, organoboron compounds have found increasing applications in the fields of pharmaceutical chemistry[2] and materials science.[3] Therefore, the development of efficient methods to prepare them is of even higher demand than ever.

Well established preparative methods exist for the synthesis of (monosubstituted alkenyl)(diorganyl)boranes such that these compounds have been widely applied for the synthesis of unsaturated organic compounds like allylic alcohols.[4] However, the selective preparation of both stereoisomers of (trisubstituted alkenyl)(diorganyl)boranes remains a significant challenge.[5,6] We have reported that alkynyl(triaryl)borates (aryl = Ar^1) react with aryl halides (Ar^2-X) in the presence of a palladium catalyst to afford (trisubstituted alkenyl)(diaryl)boranes, in which the two aryl groups (Ar^1 and Ar^2) are incorporated *cis* to each other across the resulting carbon−carbon double bond.[7] Considering the potential utility of these compounds, we embarked on the development of a complementary synthetic method for the (*E*)-isomers. In this Letter, we describe the stereoselective synthesis of (*E*)-(trisubstituted alkenyl)-9-BBNs by a pal-

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(3) (a) Entwistle, C. D.; Marder, T. B. *Chem. Mater.* **2004**, *16*, 4574. (b) Yamaguchi, S.; Wakamiya, A. *Pure Appl. Chem.* **2006**, *78*, 1413. (c) Jäkle, F. *Coord. Chem. Rev.* **2006**, *250*, 1107.

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(5) For stereoselective synthesis of (trisubstituted alkenyl)(dialkyl)boranes via addition of X-BR_2 (X = halogen and thiolate) to alkynes, see: (a) Suzuki, A. *Pure. Appl. Chem.* **1986**, *58*, 629. (b) Ishiyama, T.; Nishijima, K.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 7219.

(6) For a review of the reactions of alkynyltriorganylborate with electrophiles, giving (trisubstituted alkenyl)(diorganyl)boranes, see: Negishi, E. *J. Organomet. Chem.* **1976**, *108*, 281.

(7) (a) Ishida, N.; Miura, T.; Murakami, M. *Chem Commun.* **2007**, 4381. See also: (b) Ishida, N.; Narumi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 1279.

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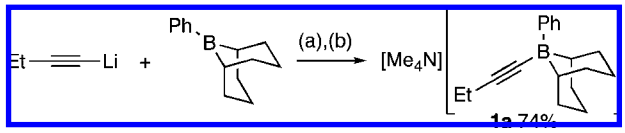
ladium-catalyzed reaction of alkynylborates with aryl halides, in which the two different aryl groups are installed *trans* to each other.

Alkynylborate **1a** was readily prepared by the reaction of Ph-9-BBN with but-1-ynyllithium in THF,[8] and subsequent cation exchange with tetramethylammonium chloride in methanol (Scheme 1). The borate **1a** is obtained as a white

Scheme 1. Preparation of Alkynylborate **1a**[a]

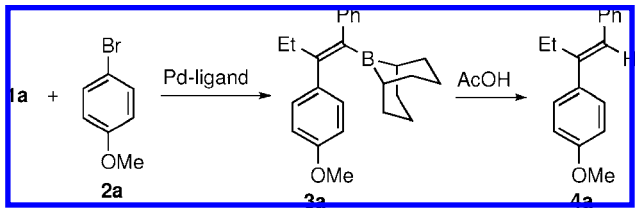


[a] Reagents and conditions: (a) THF, −78 °C to rt, 1 h. (b) Me_4NCl, MeOH, rt, 5 min.

precipitate of high purity, stable to air and moisture, and therefore, storable without any decomposition for several months.

Alkynylborate **1a** thus derived from Ph-9-BBN is preferred over the corresponding alkynyl*triaryl*borate as the starting substance from a synthetic point of view. It was subjected to the palladium-catalyzed reaction with 4-bromoanisole in the presence of various phosphine ligands (Table 1). When tri(*o*-tolyl)phosphine was em-

Table 1. Ligand Screening[a]



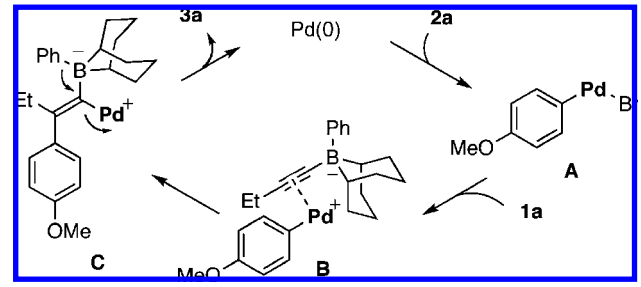
entry	ligand	yield of **4a**/ %[b]	*E*/*Z* of **4a**[b]
1	P(*o*-tol)$_3$	69	3/97
2	P(*t*-Bu)$_3$	47	17/83
3	1-[(*t*-Bu)$_2$P](biphenyl)	18	28/72
4	2-[(*t*-Bu)$_2$P](1,1′-binaphthyl)	21	67/33
5	DPEPhos	24	92/8
6	XANTPhos	73	>99/1

[a] Reaction conditions: 1.0 equiv of **1a**, 1.05 equiv of **2a**, 2.5 mol % of [PdCl(π-allyl)]$_2$, 6 mol % of ligand, toluene, 70 °C, 30 min; then AcOH, rt, 3 h. [b] Determined by GC analysis.

ployed as the ligand, the phenyl group on boron underwent 1,3-migration onto the palladium in preference to the bridgehead sp^3 carbons of the 9-BBN moiety, and the (*Z*)-isomer was stereoselectively formed, as with the case of the corresponding triphenylborate.[7a] Although we attempted to isolate the produced triorganoborane **3a**, it failed because **3a** was prone to decompose in air. Instead, **3a** was immediately hydrolyzed with acetic acid[9] to give the alkene (*Z*)-**4a** (*E*/*Z* = 3/97, entry 1). The *E*/*Z* ratio changed in favor of the (*E*)-isomer as the steric bulkiness of the monodentate phosphine increased (entries 2−4). Surprisingly, the stereochemical preference was reversed for the (*E*)-isomer (*E*/*Z* = 92/8) when bidentate ligand DPEPhos having a large bite angle was used (entry 5). Finally, it was found that XANTPhos, possessing an even larger bite angle, exclusively gave (*E*)-**4a** in 73% yield (entry 6).

Thus, the stereochemistry of the product depended strongly on the phosphine ligand employed. A proposed mechanism for the *trans*-addition reaction is shown in Scheme 2: (i)

Scheme 2. Proposed Mechanism



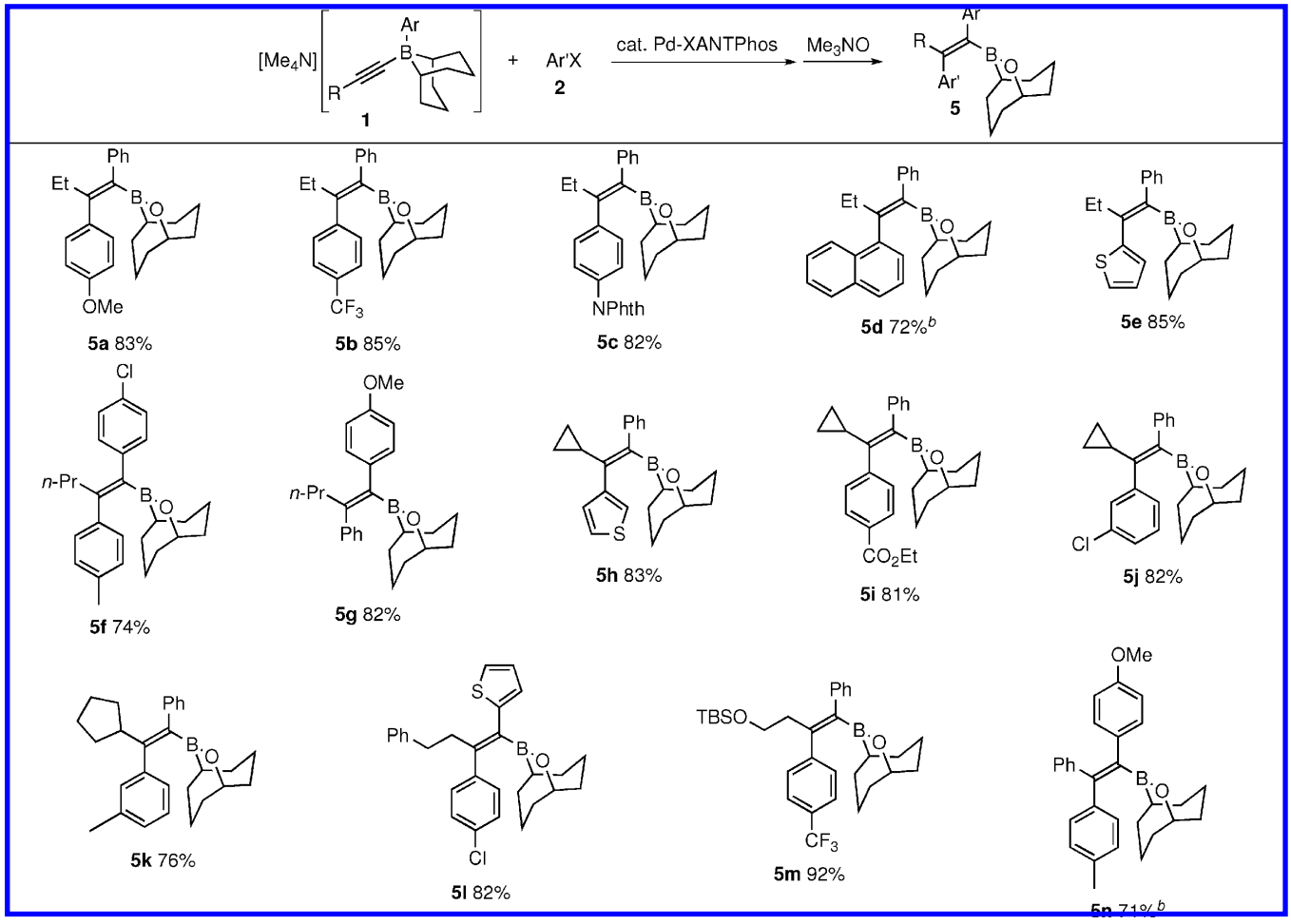
oxidative addition of 4-bromoanisole (**2a**) to palladium(0) gives arylpalladium bromide **A**, (ii) arylpalladium species **A** is coordinated by alkynylborate **1a** to form intermediate **B**, (iii) carbopalladation across the carbon−carbon triple bond occurs in a *cis* fashion to provide alkenylpalladium **C**, and (iv) a phenyl group on boron migrates to the α-carbon with inversion of stereochemistry,[10,11] resulting in the formation of *trans*-addition product **3a** with regeneration of the palladium(0).[12]

The ligand-dependent reaction pathway of the phenyl migration is explained as follows. Tri(*o*-tolyl)phosphine is relatively less stereodemanding and, when located around the palladium center, provides enough space for the phenyl group on boron to undergo 1,3-migration to palladium (Scheme 4). On the other hand, a bulky bidentate ligand XANTPhos likely disfavors the 1,3-phenyl migration from boron to palladium. Instead, the direct 1,2-migration of the phenyl group from boron onto the α-carbon dominates,[10] giving *trans*-addition product. Tri(*tert*-butyl)phosphine and Buchwald-type ligands, which are intermediates between tri(*o*-tolyl)phosphine and XANTPhos in sterics, may permit both of these pathways, resulting in a mixture of *E*/*Z* isomers.

Next, we tried to isolate the addition product in the form of an alkenylborane, which was applicable to subsequent synthetic transformations rather than losing a carbon−boron linkage by hydrolysis. When the reaction mixture was directly subjected to a migrative oxidation reaction with

(8) Whiteley, C. G. *S. Afr. J. Chem*. **1982**, *35*, 9.
(9) The protonolysis of alkenylboranes with acetic acid proceeds in a stereospecific fashion: Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc*. **1959**, *81*, 1512.

Scheme 3. Synthesis of Borinic Esters[a,b]

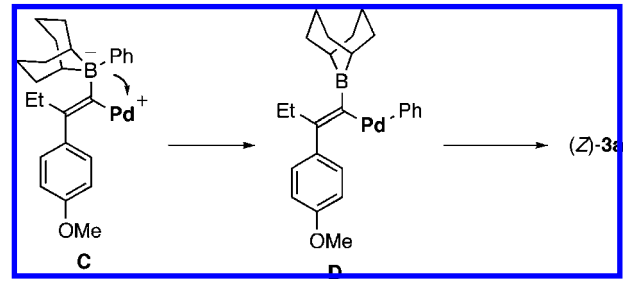


[a] Reaction conditions: 1.0 equiv of alkynylborate **1**, 1.05 equiv of aryl halide **2**, 1 mol % of (xantphos)PdCl(π-allyl), toluene, 70 °C, 30 min; then 1.5 equiv of Me_3NO, DCM, rt, 2 h. Isolated yields were shown. The major isomers shown in the table were observed with >95/5 ratio by NMR analysis. The stereochemistries of **5g** and **5m** were determined by NOE analysis and those of other borinic esters **5** were assumed by analogy. [b] Aryl iodide was used.

trimethylamine-*N*-oxide, (trisubstituted alkenyl)borinic ester **5a** in which the bridgehead sp^3 carbon migrated onto oxygen was obtained stereoselectively.[13] The resulting borinic ester (*E*)-**5a** was stable enough to be isolated by column chromatography on silica gel and could be stored without any decomposition for a longer period of time than 1 month. Most importantly, this reagent could be employed for subsequent carbon−carbon bond forming reactions (vide infra).

A wide variety of borinic esters were synthesized with use of the palladium/XANTPhos system followed by migrative oxidation with trimethylamine-*N*-oxide (Scheme 3). Aryl halides having either an electron-donating or an electron-withdrawing substituent gave the corresponding borinic esters in good yields (**5a** and **5b**). Phthalimide (**5c**), chloro (**5f**, **5j**, and **5*l***), and ester (**5i**) groups remained intact under the reaction conditions. A sterically demanding aryl iodide was also reactive (**5d**). In addition to the substituted phenyl groups, 2- and 3-bromothiophene afforded the desired product in good yield (**5e** and **5h**). Primary alkyl (**5a** to **5g**, **5*l***, and **5m**), secondary alkyl (**5h** to **5k**), and aryl (**5n**) groups can be used as the substituent of the alkynyl moiety. The scope of the aryl group on boron was also broad; electron-rich (**5g** and **5n**) and -deficient (**5f**) phenyl and thienyl (**5*l***) groups successfully participated in the migration reaction.

Scheme 4. 1,3-Migration of Aryl Group

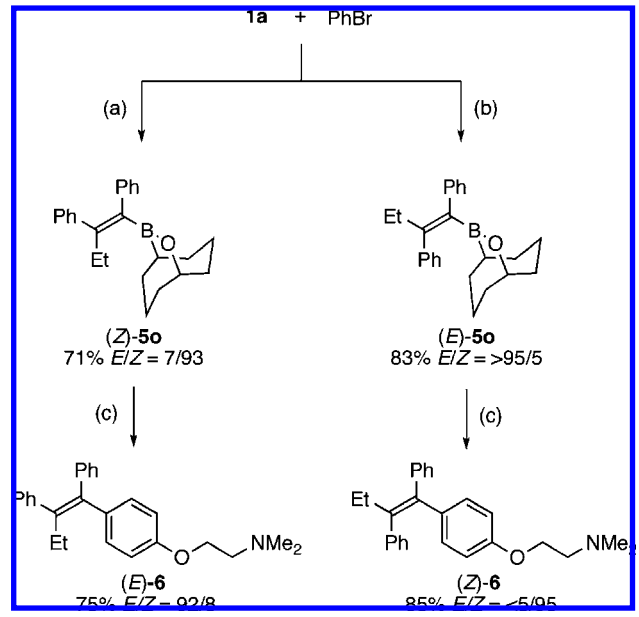


Finally, we applied this reaction to the synthesis of both isomers of Tamoxifen (Scheme 5), which has been in clinical

use for cancer treatment.[14,15] The reaction of **1a** with bromobenzene with the palladium/tri(*o*-tolyl)phosphine catalyst followed by oxidation with trimethylamine-*N*-oxide gave borinic ester (*Z*)-**5o** (71% yield, *E*/*Z* = 7/93). On the other hand, the corresponding (*E*)-isomer was stereoselectively obtained in 83% yield (*E*/*Z* = >95/5) when the reaction of **1a** with bromobenzene was carried out with the palladium/XANTPhos calatyst, the loading of which could be decreased even to 0.1 mol %. The Suzuki−Miyaura coupling reaction of each stereoisomer of **5o** with 1-bromo-4-[2-(*N*,*N*-dimethylamino)ethoxy]benzene (**2b**) afforded Tamoxifen (**6**) with retention of each stereochemistry. Thus, the present study made it possible to synthesize either stereoisomer of tetrasubstituted olefins[16] starting from the same substances by choice of the appropriate ligand.

In summary, we have developed a new catalyst system for the palladium-catalyzed reaction of alkynylborates with aryl halides, which produces (*E*)-(trisubstituted alkenyl)boranes stereoselectively. With both stereoisomers being available, the reinforced palladium-catalyzed reaction of alkynylborates serves as an authentic method for the synthesis of (trisubstituted alkenyl)boron compounds.

Scheme 5. Synthesis of Tamoxifens[a]



[a] Reagents and conditions: (a) 1 mol % of (*o*-tol)$_3$PPdCl(π-allyl), toluene, 70 °C, 30 min; then 1.5 equiv of Me_3NO, DCM, rt, 2 h. (b) 0.1 mol % of (xantphos)PdCl(π-allyl), toluene, 70 °C, 5 h; then 1.5 equiv of Me_3NO, DCM, rt, 5 h. (c) 1.05 equiv of 4-BrC_6H_4[O$(CH_2)_2$NMe_2] (**2b**), 2.5 mol % of Pd$(OAc)_2$, 5 mol % of SPhos, K_3PO_4, THF, 60 °C, 12 h for (*E*)-**5o**, 24 h for (*Z*)-**5o**.

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

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(10) For substitutive 1,2-migration from boron to the α-carbon with inversion of stereochemistry, see: Köbrich, G.; Merkle, H. R. *Angew. Chem., Int. Ed.* **1967**, *6*, 74.

(11) Inversion of the stereochemistry was also observed in the palladium-catalyzed cross-coupling reaction of 2-bromo-1,3-dienes with organozinc reagents: Zeng, X.; Hu, Q.; Qian, M.; Negishi, E. *J. Am. Chem. Soc.* **2003**, *125*, 13636.

(12) An alternative mechanism is conceivable; the arylpalladium bromide **A** acts as an electrophile to place the palladium on the carbon β to boron and induces migration of a phenyl group on boron to the α-carbon. A similar mechanism has been assumed for analogous reactions of alkynylborates with alkyl halides, most of which lacked in stereoselectivity. The high stereoselectivity obtained in the present reaction led us to favor the mechanism proposed in the text.

(13) Soderquist, J. A.; Najafi, M. R. *J. Am. Chem. Soc.* **1986**, *51*, 1330.

(14) Wiseman, H. *Tamoxifen: Molecular Basis of Use in Cancer Treatment and Prevention*; Wiley: Chichester, U.K., 1994.

(15) For representative Tamoxifen syntheses, see: (a) Millar, R. B.; Al-Hassan, M. I. *J. Org. Chem.* **1985**, *50*, 2121. (b) Potter, G. A.; McCague, R. *J. Org. Chem.* **1990**, *55*, 6184. (c) Brown, S. D.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 7076. (d) Studemann, T.; Knochel, P. *Angew. Chem., Int. Ed.* **1997**, *36*, 93. (e) Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. *Org. Lett.* **2003**, *5*, 2989. (f) Itami, K.; Kamei, T.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2003**, *125*, 14670. (g) Shimizu, M.; Nakamaki, C.; Shimono, K.; Schelper, M.; Kurahashi, T.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 12506. (h) Nishihara, Y.; Miyasaka, M.; Okamoto, M.; Takahashi, H.; Inoue, E.; Tanemura, K.; Takagi, K. *J. Am. Chem. Soc.* **2007**, *129*, 12634.

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