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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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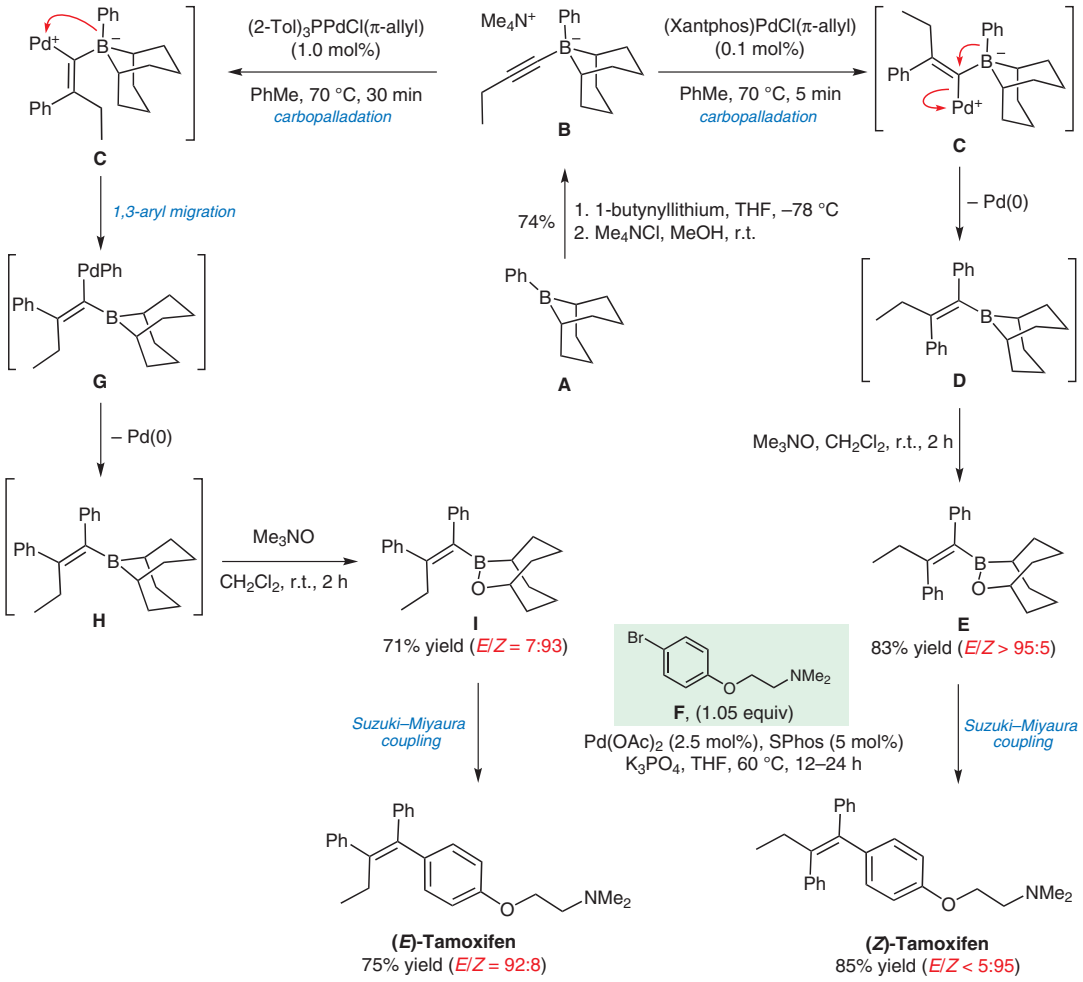
Synthesis of (*E*)- and (*Z*)-Tamoxifen



Significance: (*Z*)-Tamoxifen is used for the treatment of estrogen receptor positive breast cancer. The synthesis depicted features a *syn*-carbopalladation of alkynyl borate **B** followed by a 1,2-aryl migration (**C** → **D**) to generate a trisubstituted alkenylborane in high yield and stereoselectivity. Oxidation of the alkenylbornane **D** with Me_3NO afforded the alkenylborinic ester **E** that participated in an efficient Suzuki–Miyaura coupling to give (*Z*)-tamoxifen.

Comment: The fate of the *syn*-carbopalladation product **C** depended on the ligand. When the ligand was small [$(2\text{-Tol})_3P$], a 1,3-aryl migration took place (**C** → **G**) to generate the alkenylborane **H** after reductive elimination. Alkenylborane **H** was converted into (*E*)-tamoxifen as shown. The borate derived from **B** is stable towards air and moisture. A further 14 examples of the synthesis of alkenylborinic esters via the 1,2-aryl migration pathway are presented.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

tamoxifen
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Suzuki–Miyaura coupling
borinic esters
alkynyl borates
palladium