A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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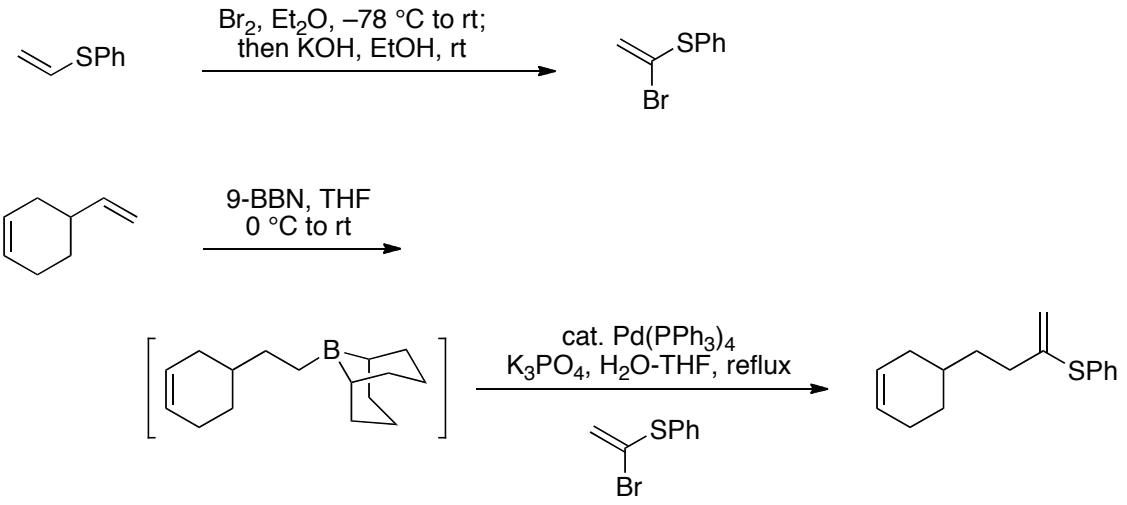
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Discussion Addendum for:

PALLADIUM(0)-CATALYZED REACTION OF 9-ALKYL-9-BORABICYCLO[3.3.1]NONANE WITH 1-BROMO-1-PHENYLTHIOETHENE: 4-(3-CYCLOHEXENYL)-2-PHENYLTHIO-1-BUTENE



Prepared by Norio Miyaura.[†]

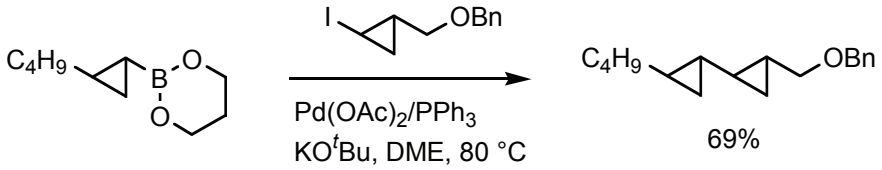
Original article: Miyaura, N.; Ishiyama, T.; Suzuki, A. *Org. Synth.* **1993**, *71*, 89.

The cross-coupling reactions of organoboron compounds have proved to be a general method for a wide range of selective carbon-carbon bond forming reactions.[1] In 1989, the cross-coupling reaction of 9-alkyl-9-BBN with 1-alkenyl and aryl halides or triflates was found to proceed smoothly in the presence of $PdCl_2$(dppf) and $K_3PO_4 \cdot nH_2O$.[2] This coupling reaction of B-alkyl compounds has been reviewed.[3,4] The reaction is limited to *primary* alkylboranes; hydroboration of terminal alkenes with 9-BBN is the most convenient way to furnish the desired boron reagents. The reaction is catalyzed by $PdCl_2$(dppf),[2] $PdCl_2$(dppf)/$2Ph_3As$,[5] or other palladium-phosphine complexes in the presence of a base (Table 1). Since the presence of water greatly accelerates the reaction, the use of the hydrate of inorganic bases such as $K_3PO_4 \cdot nH_2O$ (entry 1) or aqueous bases (entries 2 and 4) is generally recommended.[5] On the other hand, solid sodium methoxide added to 9-alkyl-9-BBN dissolves in THF by forming the corresponding ate-complex, which enables room temperature coupling under non-aqueous

conditions (entries 3 and 5).[2] Treatment of 9-methoxy-9-BBN with *primary*-alkyllithiums is an alternative for *in situ* preparation of analogous boron ate-complexes.[6] The presence of KBr (1 equiv) is often critical to prevent decomposition of the catalyst for reactions of aryl and 1-alkenyl triflates (entry 6).[7]

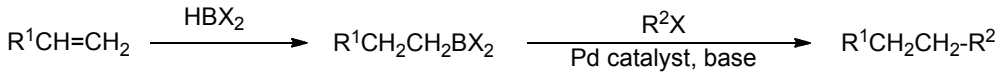
Sp^3-sp^3 bond formation between two alkyl derivatives has been much less successful among the possible combinations of different-type nucleophiles and electrophiles. Difficulties arise from the oxidative addition of haloalkanes (RCH_2CH_2X) to a palladium(0) complex due to accompanying formation of $RCH{=}CH_2$ and RCH_2CH_3 and from the susceptibility of alkylpalladium(II) intermediates to β-hydride elimination.[8] In spite of these difficulties, sp^3-sp^3 bond formation occurs smoothly between *primary*-alkyl halides and *primary*-alkylboron compounds where each reactant possesses β-hydrogen (entries 8 and 9).[9] The coupling with secondary alkyl halides has been limited to cyclopropyl iodides.[10,11]

The reactions of the corresponding alkylboronic acids and $[alkylBF_3]K$[12] are significantly slower than that of trialkylboranes, but methylboroxine $(MeBO)_3$ or methylboronic acid alkylates bromoarenes with a common palladium/triphenylphosphine catalyst (entry 10).[13] Analogous reactions of alkylboronic acids possessing β-hydrogen are achieved by the use of Qphos (**2**) for aryl or 1-alkenyl bromides, triflates and chlorides (entry 11),[14] a dppf complex for iodides, bromides and triflates,[12,15] and N-cyclic carbene (**1**)[16] for arene diazonium salts. These reactions are limited to use for *primary*-alkylboronic acids; however, cyclopropylboronic acid derivatives alkylate aryl and 1-alkenyl halides or triflates[17] and acyl chlorides[18] without loss of stereochemistry of the cyclopropane ring (eq 1).

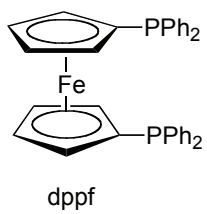


(1)

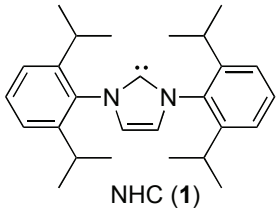
Table 1. Reaction Conditions for Coupling of primary-Alkylboron Derivatives



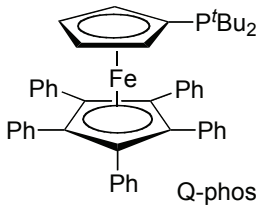
entry	BX_2=	R^2-X	catalyst/base/solvent	temp/°C	ref.
1	9-BBN	alkenyl, aryl I, Br	$PdCl_2$(dppf), $K_3PO_4 \cdot nH_2O$, DMF	rt-50	[4,6,7]
2	9-BBN	alkenyl, aryl I, Br	$PdCl_2$(dppf), NaOH, THF-H_2O	rt-reflux	[4]
3	9-BBN	alkenyl, aryl I, Br	$PdCl_2$(dppf), NaOMe, THF	rt-reflux	[4]
4	9-BBN	alkenyl, aryl I	$PdCl_2$(dppf)/2$AsPh_3$, Cs_2CO_3, DMF-H_2O	rt	[5]
5	9-BBN	aryl Cl	$Pd(OAc)_2$/NHC (**1**), KOMe, THF	reflux	[19]
6	9-BBN	alkenyl OTf	$PdCl_2$(dppf)/$AsPh_3$, Cs_2CO_3, KBr, DMF-H_2O	rt	[20]
7	9-BBN	alkenyl $OP(O)(OPh)_2$	$Pd(PPh_3)_4$, $NaHCO_3$, DMF-H_2O	50	[21]
8	9-BBN	*prim*-alkyl Br	$Pd(OAc)_2$/PCy_3, K_3PO_4, THF	rt	[9a]
9	9-BBN	*prim*-alkyl Cl	$Pd_2(dba)_3$/PCy_3, CsOH, dioxane	90	[9b]
10	$(MeBO)_3$	aryl I, Br	$Pd(PPh_3)_4$, K_2CO_3, dioxane-H_2O	reflux	[13]
11	$B(OH)_2$	*prim*-alkyl Cl	$Pd_2(dba)_3$/Qphos (**2**), K_3PO_4, toluene	100	[14]
12	BF_3K	aryl I, Br	$PdCl_2$(dppf), Cs_2CO_3, THF-H_2O	reflux	[12]



dppf



NHC (**1**)



Q-phos (**2**)

The connection of two fragments *via* the hydroboration-cross coupling sequence has found a wide range of applications in the synthesis of natural products and functional molecules,[1,3,4] including bacterial metabolites epothilone A and B,[22] ciguatoxin,[23] clinically useful 2-alkylcarbapenems,[24] and a novel class of glycomimetic compounds, aza-C-disaccharides.[25]

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Norio Miyaura was born in Hokkaido in Japan in 1946. He received his B. Eng. and Dr. Eng. from Hokkaido University. He became a Research Associate and an Associate Professor in the A. Suzuki research group, and then was promoted to the rank of Professor in the same group in 1994. He is now emeritus and a specially appointed Professor after his retirement from Hokkaido University in 2010. In 1981, he joined the J. K. Kochi group at Indiana University as a postdoctoral fellow to study the epoxidation of alkenes catalyzed by metal-salen complexes. His current interests are mainly in the field of metal-catalyzed reactions of organoboron compounds, with emphasis of applications to organic synthesis such as catalyzed hydroboration, palladium-catalyzed cross-coupling reactions of organoboronic acids, rhodium- or palladium-catalyzed conjugate addition reactions of arylboronic acids, and addition and coupling reactions of diborons and pinacolborane for the synthesis of organoboronic esters.