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Synthetic studies via the cross-coupling reaction of organoboron derivatives with organic halides

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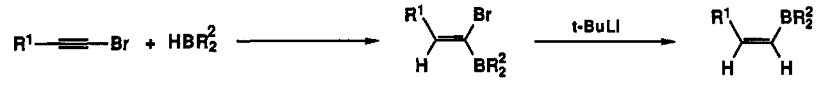
Abstract - Previously, we reported the palladium-catalyzed cross-coupling reaction of 1-alkenylboron compounds with various vinylic or aryl halides in the presence of base to provide corresponding coupling products in good yields, stereo- and regioselectively. The recent progress of such reactions is discussed. Most recently, it has been found that B-alkylorganoboranes react readily with vinylic halides or haloarenes in the presence of special palladium catalyst and base. Furthermore, even the most difficult cross-coupling of B-alkyl-9-BBN with alkyl iodides has been demonstrated to proceed smoothly to give coupling alkane derivatives in moderate yields under special conditions. Finally, it will be discussed that B-alkyl-9-BBN derivatives react with iodoalkanes under carbon monoxide atmosphere in the presence of potassium phosphate and a catalytic amount of $Pd(PPh_3)_4$, yielding unsymmetrical ketones in excellent yields. The reaction is extremely accelerated by irradiation of light.

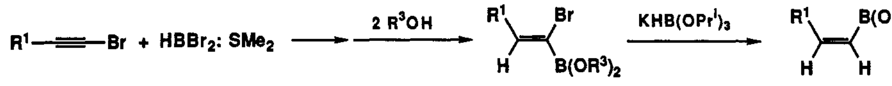
RECENT PROGRESS OF CROSS-COUPLING REACTION USING 1-ALKENYLBORANES

Previously we reported a simple and versatile synthesis leading to conjugated (E,E)-, (E,Z)-, (Z,E)-, and (Z,Z)-alkadienes (ref. 1) via a cross-coupling reaction of (E)- or (Z)-1-alkenyldisiamylboranes or 2-[(E)-1-alkenyl]-1,3,2-benzodioxaboroles (B-1-alkenylcatecholboranes) with either (E)- or (Z)-1-alkenyl halides in the presence of a catalytic amount of palladium catalyst and base in benzene. The coupling with (E)-1-alkenylboronic acids or their esters prepared by hydroboration of alkynes with catecholborane always gives the expected dienes in 80-90% yields, while the coupling reactions with (Z)-1-alkenyldisiamyl- (**Ia**) or (Z)-1-alkenyldicyclohexylboranes (**Ib**) give relatively poor yields of the coupling products (**4**), less than 50%. One of the major reasons for this difficulty appears to be due to the side reaction arising from the two alkyl groups on boron atom. In order to overcome this, we have attempted to use (Z)-1-alkenylboronates (**3**), first prepared by Brown and Imai (ref. 2). The reactions between 1-alkenyl halides or aryl halides and such (Z)-1-alkenylboronates (**3**) proceed smoothly to give corresponding (E,Z)- and (Z,Z)-alkadienes or arylated alkenes in excellent yields stereo-and regioselectively (eq. 3, ref. 3). For instance, the reaction of diisopropyl (Z)-1-hexenylboronate with phenyl iodide affords (Z)-1-phenyl-1-hexene in 98% yield with high isomeric purity (>97%).



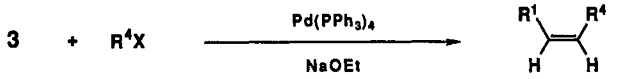
(1)

1a : R^2 = siamyl
1b : R^2 = cyclohexyl



(2)

2 **3**

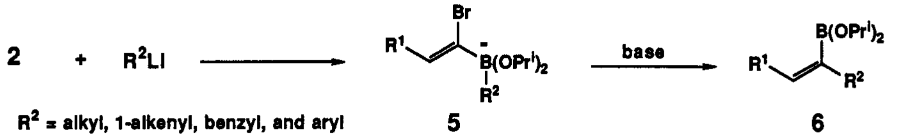


R^4 = 1-alkenyl and aryl
X = Br, I

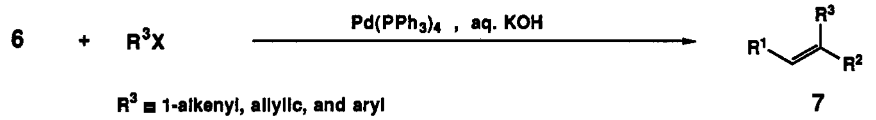
(3)

4

As an extension of the synthetic applications of intermediates (**2**), we have tried and found that the reaction of **2** with organolithiums takes place readily to give (E)-(1-alkyl-1-alkenyl)boronates (**6**). The cross-coupling reaction of these boronates with various organic halides also proceeds smoothly under similar conditions to povide almost exclusively the corresponding trisubstituted alkenes (**7**) stereoselectively (eqs.4 and 5, ref. 4).

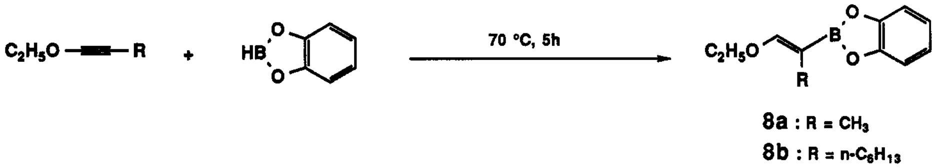


(4)

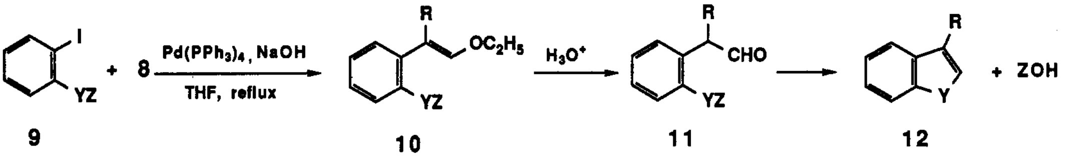


(5)

Cyclodehydration of 2-hydroxy- or 2-aminobenzeneethanal derivatives is known as a general procedure for the synthesis of benzo-fused heteroaromatic compounds such as 1-benzofurans and indoles (ref. 5). Although numerous modifications of this method have been studied, the mejor difficulty seems to be the lack of a general synthesis of required *ortho*-functionalized areneethanals. In order to employ our cross-coupling reaction for the synthesis of areneethanals, the reaction of (1-ethoxy-1-alken-2-yl)boranes (**8**), prepared by the method described in eq. 6, with *ortho*-functionalized aryl halides has been examined and discovered that such a reaction occurs readily to give expected products (**10**) in excellent yields. The hydrolysis and the subsequent ring closure afford corresponding benzo-fused heteroaromatic compounds (eq. 7, ref. 6).



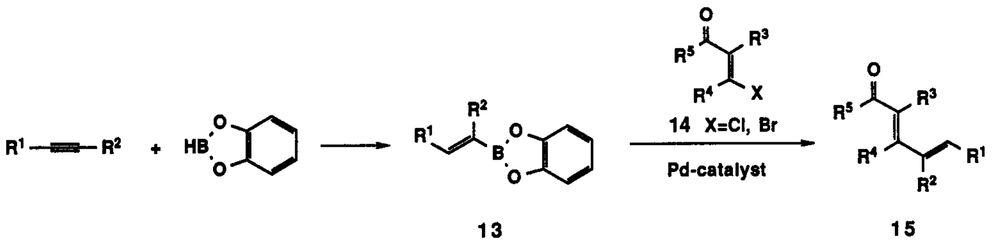
(6)



(7)

The stereo- and regioselective synthesis of 1,3,5-alkatrienes has been carried out through the palladium-catalyzed cross-coupling reaction of (E)- or (Z)-1-alkenylboronates with (E)- or (Z)-2-bromo-1-phenylthio-1-alkenes, followed by the reaction with Grignard reagents in the presence of nickel catalyst (ref. 7).

Since 1-alkenylboronates such as **13** are quite inert toward many functionalities including carbonyl group, the coupling reaction can be carried out without any protection of these groups. On the other hand, the reaction only proceeds in the presence of base. Consequently, vinylic halides with the functional groups sensitive to base, such as haloenone (**14**) may cause difficulties. In the cross-coupling between **13** and **14**, it has been found that relatively weak bases such as sodium acetate and triethylamine are effective in obtaining high yields of the coupling products **15** (ref.8).

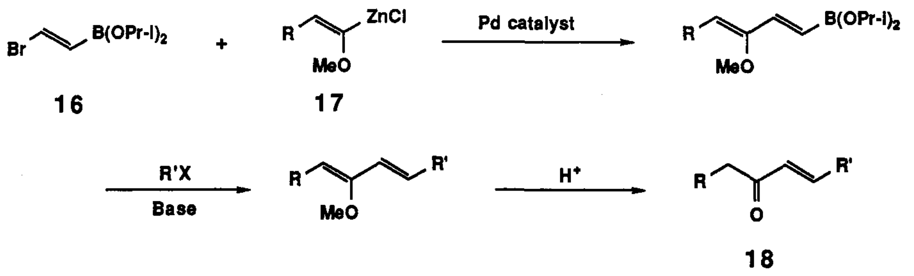


(8)

Similarly (2E,4E)-, (2Z,4E)-, and (2E,4Z)-alkadienoates can be synthesized in high yields by the cross-coupling of ethyl (E)-3-bromoacrylate, methyl (E)-3-bromo-2-methylpropenoate, ethyl (Z)-3-bromocrotonate, 1-bromo-2-(ethoxycarbonyl)cyclohexene, and 4-bromocumarin with 2-[(E)-1-alkenyl]-1,3,2-benzodioxaboroles or diisopropyl (Z)-1-hexenylboronate in the presence of 3 mol% of $Pd(OAc)_2$, 6 mol% of PPh_3, and 2 equivalents of Na_2CO_3 or

K_2CO_3 in alcoholic solvents while retaining the original configuration of the double bonds in β-bromo esters and 1-alkenylboronates (ref.9).

The palladium catalyzed stepwise cross-coupling reaction of (E)-(2-bromoethenyl)diisopropoxyborane (**16**) readily available by the bromoboration of acetylene, with α-alkoxyalkenylzinc chlorides (**17**) and organic halides, R'X gives α,β-unsaturated ketones directly in good yields with high isomeric purity (eq. 9, ref. 10).

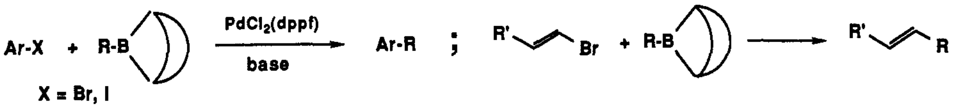


16 **17** **18**

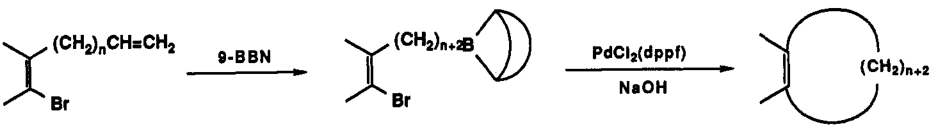
(9)

PALLADIUM CATALYZED CROSS-COUPLING REACTION OF B-ALKYL-9-BBN DERIVATIVES

Although the palladium-catalyzed cross-coupling reactions of 1-alkenyl- and arylboron compounds with organic halides proceed readily and stereo- and regioselectively to give expected compounds in high yields, organoboranes with alkyl groups on boron have not been used successfully for the coupling under similar conditions. Most recently we have found that the reaction between B-alkyl-9-borabicyclo[3.3.1]nonanes (B-R-9-BBN) and 1-halo-1-alkenes or haloarenes in the presence of a catalytic amount of dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) [$PdCl_2$(dppf)] and base, such as sodium hydroxide, potassium carbonate, and phosphate gives the corresponding alkenes or arenes in excellent yields (eq.10, ref. 11). Because the reaction is tolerant of a variety of functionalities on either coupling partner, stereochemically pure functionalized alkenes and arenes can be obtained under mild conditions. The utility of the reaction was demonstrated by the stereoselective synthesis of 1,5-alkadienes and the extension of side chain in a steroid. The hydroboration of haloakadienes, followed by the intramolecular cross-coupling, gave a short-step procedure for the synthesis of cycloalkenes, benzo-fused cycloalkenes, and exocyclic alkenes (eq.11)



(10)

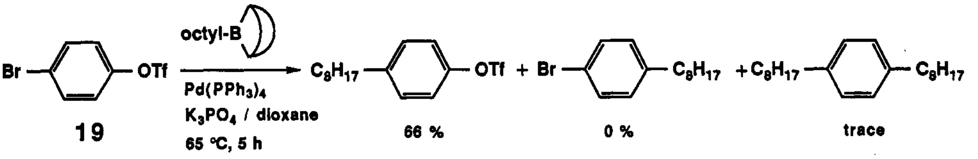


(11)

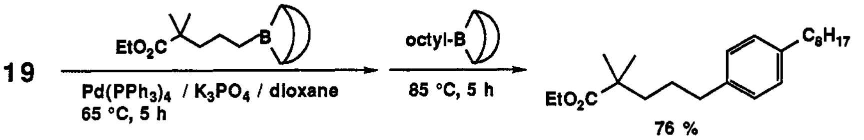
The reaction of B-alkyl-9-BBN derivatives with 1-bromo-1-phenylthioethene or (E)- and (Z)-2-bromo-1-phenylthio-1-alkenes takes place readily in the presence of $Pd(PPh_3)_4$ and sodium hydroxide to afford stereodefined vinylic sulfides in excellent yields (ref.12). Such vinylic sulfide derivatives are well-known as efficient building blocks for the synthesis of stereodefined double bounds by sequential cross-coupling reaction with Grignard reagents. Consequently, the combination of these two reactions provides a convenient synthesis of stereodefined conjugated polyenes.

The reaction with B-alkyl-9-BBN derivatives occurs readily, whereas the use of boronic acid esters as coupling partners have been desired since such compounds are easily prepared and are stable rather than B-alkyl-9-BBN compounds. As reported previously, the base is essential for the success of the coupling reaction of alkylboranes (refs. 11 and 12). However, the coupling reaction of boronic esters does not proceed smoothly in the presence of usual bases such as sodium carbonate, hydroxide, and methoxide. Fortunately, it has been proved that the cross-coupling of alkylboronic acid esters with 1-alkenyl or aryl halides is successfully catalyzed by $PdCl_2$(dppf) or $Pd(PPh_3)_4$ in the presence of thallium(I) hydroxide or carbonate to give alkenes of arenes in good yields (ref.13). The coupling reaction of arylboronic esters with aryl halides under similar conditions provides biaryls.

Most recently, it has become apparent that the palladium-catalyzed coupling reactions of 1-alkenyl-, aryl-, and alkylboron compounds with aryl or 1-alkenyl triflates, instead of using corresponding organic halides take place with ease to give expected coupling products in high yields under mild conditions (ref.14). The reactivity of triflates and halides in the reaction with organoboron compounds may decrease in the order of I > Br > OTf >> Cl. Thus, highly selective coupling of B-octyl-9-BBN with the C-Br bond in 4-bromophenyl triflate (**19**) was observed (eq. 12). The sequential cross-coupling of **19** with two B-alkyl-9-BBN derivatives obtained from two different alkenes affords the unsymmetrically disubstituted benzene derivative (eq.13).

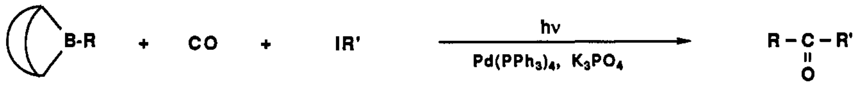


(12)



(13)

Palladium complexes are employed to catalyze the reactions of a wide variety of electrophiles, including aryl, vinylic, allylic, benzylic, and 1-alkynyl halides with not only organoboron compounds but also organo-main group metal compounds (ref.15). Notably missing from the list are the alkyl electrophiles, which are widely recognized that after oxidative addition of alkyl electrophiles, β-hydride elimination would rapidly occur (ref. 15). Castle and Widdowson previously reported that Pd(dppf), formed *in situ* by the reduction of $PdCl_2$(dppf) with 2 equivalents of DIBAL, effectively catalyzes the cross-coupling of alkyl iodides with Grignard reagents (ref.16). Nevertheless, Yuan and Scott have most recently presented that Pd(dppf) and $PdCl_2$(dppf) do not act as efficient catalysts for the coupling of alkyl halides with Grignard reagents, and reduction products from alkyl halides are most commonly obtained and the β-hydride elimination occurs in some cases (ref.17). On the other hand, we have observed that the reaction system of dioxane/$Pd(PPh_3)_4$/K_3PO_4 gives good results for the cross-coupling reaction between B-alkyl-9-BBN and iodoalkanes to provide corresponding coupling products in moderate yields. (ref.18). This is the first reported palladium-catalyzed coupling of unactivated alkyl electrophiles. It has been discovered that B-alkyl-9-BBN derivatives react with iodoalkanes under carbon monoxide atmosphere in the presence of K_3PO_4 and a catalytic amount of $Pd(PPh_3)_4$ yielding unsymmetrical ketones directly in good yields. The reaction is extremely accelerated by irradiation of light (eq.14, ref.19).



(14)

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