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Suzuki-Type Cross Coupling Reactions Using Palladium-Water Soluble Catalyst. Synthesis of Functionalized Dienes.

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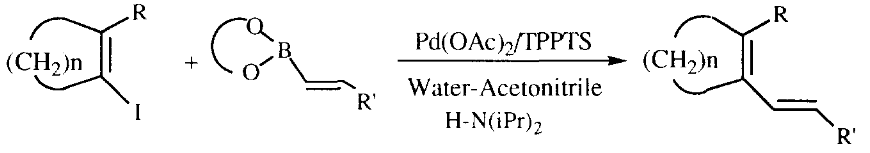
Keywords : Dienes, Trienes, Palladium aqueous catalyst, Cross-Coupling.

Abstract : The palladium(0) catalyzed cross-coupling of boronic acids or esters conducted with a water soluble catalyst in the presence of organic base allows under mild condition the production of functionalized dienes.(60-90% yield).

The palladium-catalyzed cross-coupling reaction of organometallic reagents with organic halides has become an important synthetic methodology for regio- and stereoselective bond formation between unsaturated carbon atoms. The versatility of the method is underscored by the possibility of using organometallics such as Zn, Al or Zr for the coupling with a broad range of alkenyl, alkynyl or arylhalides. One particular version on this theme the Suzuki's coupling[1] of alkenyl boranes with vinylic or arylic halides has been used extensively in organic synthesis.[2,3]

In previous publications, we have shown that the palladium-water soluble catalyst prepared *in situ* from palladium(II) acetate and TPPTS is a useful and pratical catalytic system for various cross coupling reactions and deprotection of Alloc group using π-allyl palladium methodology. [4,5]

Recently, we have investigated the palladium functionalized catalyzed cross-coupling reaction of alkenyl boronates and boronic acids with alkenyl iodides using the Pd(TTPTS)$_n$ [6] prepared *in situ*.

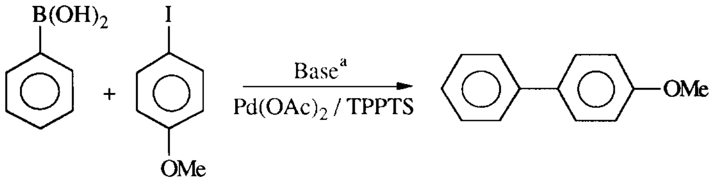


Under the classical reaction conditions this catalytic palladium cross coupling requires two equivalents of base such as potassium hydroxide [2], thallium hydroxide.[7] In the search of reaction conditions using Pd/TPPTS as catalyst a number of different bases were tried as shown in table 1.[8]

We initially examined the cross-coupling of phenyl boronic acid with p-iodo anisole under aqueous conditions (water-acetonitrile). Inorganic bases are generally inefficient (entries 1, 2, 3).

However organic bases such as triethylamine and diisopropylamine lead to the expected biphenyl product in good yield (entries 4, 5). A higher yield was obtained with diisopropylamine than with triethylamine, so diisopropylamine was employed in subsequent cross-coupling reactions.

Table 1 - Cross-coupling of Phenylboronic Acid with p-Iodo anisole in the Presence of Various Bases.



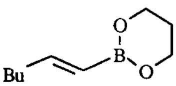
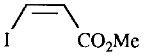
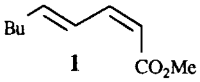
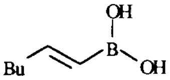
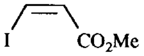
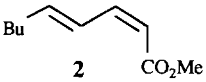
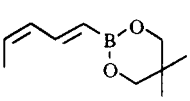
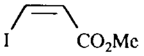
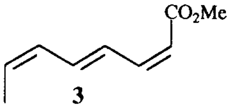
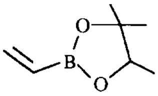
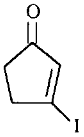
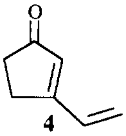
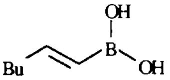
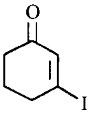
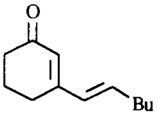
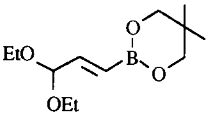
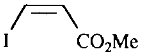
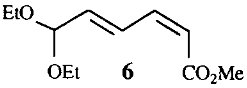
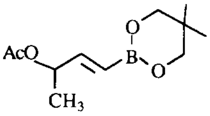
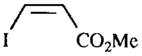
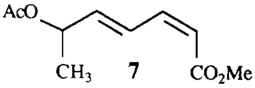
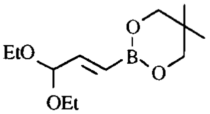
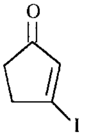
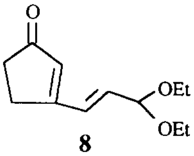
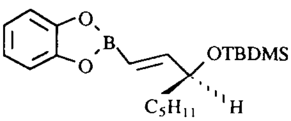
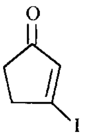
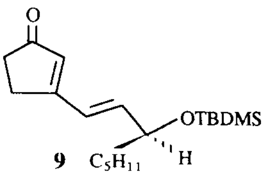
Entry	Base	Time (h)	starting material[b](%)	Yield(%)
1	K_2CO_3	1.8	95	-
2	$Ba(OH)_2$	24	74	-
3	Cs_2CO_3	2.5	69	-
4	Et_3N	72	≈0	64[c]
5	iPr_2NH	72	6	84[c]

[a]Reactions carried out in acetonitrile / water 3:1 and 2.5 mole% catalyst,[b] Estimated by NMR, [c] Isolated

The scope of the coupling was evaluated by investigating a variety of functionalized alkenyl boronic esters[9] with (Z) methyl-3-iodo propenoate as well as 3-iodocyclopentenone and 3-iodocyclohexenone. In general the cross-coupling reaction conducted in water-acetonitrile in the presence of vinyl boronate or acid afford coupled product in good to excellent yields as shown in table 2.[10] The nature of the boronic derivatives, boronic acid or ester, did not seem affect greatly the yield of coupled product (entries 1, 2, 5).

Interesting features include coupling with retention of Z olefin geometry and formation of functionalized dienes (entries 1, 2, 6) and trienes (entry 3). So the reaction of (1E,3Z) pent-1,3-dienyl-1,3,2,-dimethyldioxaborolane with (Z) methyl-3-iodopentenoate afforded the (2Z,4E,6Z) methyloct-2,4,6-trienoate. In the same way, under the standard conditions, the coupling of 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane with 3-iodocyclopentenone gave 3-(ethenyl) cyclopentenone. Interestingly under these conditions the chemoselective cross-coupling of vinylic boronic esters containing an allylic acetate or acetal moiety with (Z) methyl-3-iodo acrylate as well as 3-iodocyclopentenone occurs in acceptable yields (entries 6, 7, 8). The coupling of an alkenyl boronate having a chiral protected allylic alcohol with 3-iodocyclopentenone was also successfully accomplished under these aqueous conditions in 60% yield (entry 9).

Table 2 - Cross-coupling of Alkenyl Boron Reagents with Iodoalkenes using Pd/TPPTS formed *in situ*.[a]

Entry	Organoboron Reagent	Alkenyl iodide	Product	Yield[b] %
1			 **1**	80
2			 **2**	72
3			 **3**	70
4			 **4**	68
5			 **5**	95
6			 **6**	70
7			 **7**	60
8			 **8**	90
9			 **9**	60

a) The reactions are conducted at room temperature. b) Isolated yields

In summary the aqueous palladium catalyzed Suzuki's coupling displays an interesting versatility. It occurs under mild conditions and from the preparative view point these conditions have some advantages for the preparation of fragile α, β unsaturated esters with (Z) geometry. In addition, under these conditions the water soluble catalyst is cleanly eliminated.

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References and notes

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2 For recent reviews see : Suzuki, A.; *Pure and Appl. Chem.*, **1991**, *63*, 419-422; Vaultier, M. and Carboni, B.; Comprehensive Organometallic Chemistry Ed., II, G. Willamson Edit., Vol. 11, in Press.

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6 TPPTS : (m. sulfonated triphenylphosphine)

7 Uenishi, J. ; Beau, J.M. ; Armstrong, R.W. and Kishi, Y. ; *J. Am. Chem. Soc.* **1987**, *109*, 4756-4758

8 To our knowledge only few examples of palladium-catalyzed coupling of aryl halides with aryl boronic esters or acids in aqueous solution using preformed water soluble catalyst have been described. ; Wallow T.I., Novak, B.M. *J. Am. Chem. Soc.*, **1991**, *113*, 7411-7412; Casalnuovo, A.L., Calabrese, J.C., *J. Am. Chem. Soc.*, **1990**, *112*, 4324-4330.

9 For the preparation of some of these material see : Mazal, C. and Vaultier, M. ; *Tetrahedron Lett.*, **1994**, *35*, 3089-3090.

10 General procedure : All reactions were carried out under argon atmosphere. All solvents and when applicable (i.e. to triethylamine and diisopropylamine) bases were degassed prior to use. The bore derivative (0.389 mmole) was placed in a dry tube and acetonitrile (3mL) was added. To the solution were additionned the substrate, a vinylic or arylic iodide (0.389 mmole), water (1mL) and 2.5 eq. of base. Finally were added 2.5 mole % $Pd(OAc)_2$ and 5 mole % TPPTS (30 %) w/w solution in water). The reactions were normally followed by TLC but in some cases by GC. At the end, the reaction mixture was diluted with water, extracted with ether and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residu was purified by flash chromatography.

Selected Spectral data:
3: IR (film) : 1710, 1610, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.84 (dd, 3H, J = 7.2, 1.6 Hz); 3.73 (s, 3H); 5.66 (d, 1H, J = 10 Hz); 5.77 (dq, 1H, J = 11, 7.2 Hz); 6.21 (t, 1H, J = 11, 11 Hz); 6.66 (m, 1H); 6.81 (dd, 1H, J = 14.9, 11.5 Hz); 7.49 (dd, 1H, J = 14.9, 11.5 Hz); ^{13}C NMR ($CDCl_3$) δ: 13.71, 51.04, 116.24, 128.05, 129.18, 131.61, 136.47, 145.01; 167. **6**: IR (film) : 1720, 1645, 1605, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.22 (m, 6H); 3.63 (m, 4H); 3.74 (s, 3H); 5 (dd, 1H, J = 5.5 Hz);5.75 (d, 1H, J = 11.3 Hz); 6.02 (dd, 1H, J = 15.6, 5.5 Hz); 6.6 (m, 1H); 7.6 (dd, 1H, J = 15.6, 11 Hz); ^{13}C NMR ($CDCl_3$) δ: 15.12, 51.16, 61.37, 100, 118.7, 128.78, 139.04, 143.3, 166.5. **7**: IR (film) : 1735, 1717, 1642, 1643 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.37 (d, 3H, J = 6.6 Hz); 2.18 (s, 3H); 3.73 (s, 3H); 5.48 (m, 1H); 5.7 (d, 1H, J = 11.3 Hz); 6.02 (dd, 1H, J = 15.5, 5.8 Hz); 7.51 (dd, 1H, J = 15.5, 11.3 Hz); ^{13}C NMR ($CDCl_3$) d: 19.71, 21.10, 51.11, 69.82, 118.11, 126.52, 141.71, 143.57, 166.41, 170.07. **9**: $[\alpha]_D$ -10.27 (c=0.545, dioxane); IR (film) 1702, 1671, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.04 (s, 3H); 0.075 (s, 3H); 0.9 (m, 12H); 1.3 (m, 6H); 1.52 (m, 2H); 2.45 (m, 2H); 2.74 (m, 2H); 4.28 (q, 1H, J = 5.5 Hz); 6.02 (s, 1H); 6.27 (dd, 1H, J = 15.7, 10.1 Hz); 6.62 (d, 1H, J = 15.7 Hz); ^{13}C NMR ($CDCl_3$) δ: -4.89, -4.54, 13.9, 18, 22.45, 26.8, 27, 31.66, 34.69, 37.77, 77.55, 124.55, 130.18, 142.83, 172, 208.

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