A Large Accelerating Effect of Tri(*tert*-butyl)phosphine in the Rhodium-Catalyzed Addition of Arylboronic Acids to Aldehydes

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The addition of a metal−carbon bond to the carbon−heteroatom double bond is a very popular reaction in main group metal reagents of lithium and magnesium, but less attention has been paid to the corresponding reaction of transition-metal compounds.[1] However, the metal-catalyzed addition reactions are of interest due to their potential application to asymmetric synthesis. We previously demonstrated the efficiency of transmetalation from boron to palladium in the cross-coupling reaction of organoboron compounds with organic electrophiles.[2] The transmetalation to rhodium provided another C−C bond-forming reaction via the 1,4-addition of aryl or 1-alkenylboronic acids to α,β-unsaturated ketones,[3] esters,[4] and amides[4] and the 1,2-addition to aldehydes[5] or *N*-sulfonylaldimines.[6] The efficiency of the protocol was recently demonstrated in similar addition reactions of potassium 1-alkenyl- and aryltrifluoroborates.[7]

Here, we report the significant effect of tri(*tert*-butyl)-phosphine in accelerating the addition of aryl- and 1-alkenylboronic acids to aldehydes even at room temperature (Scheme 1).

A series of rhodium(I)/phosphine complexes in situ prepared from $Rh(acac)(coe)_2$ (coe = cyclooctene)[8] and the representative phosphines revealed the effects of bidentate phosphines (entries 1−8), basicity of monophosphines (entries 9−16), and stoichiometry of ligand on the rhodium metal (entries 15−17) (Table 1).

Preliminary results[5] indicated that the reaction is accelerated by the bidentate phosphine complexes having a large P−Rh−P angle[9] such as dppf, but the monophosphine complexes result in significantly low yields when using 3 equiv of phosphine to the rhodium metal. However, a reinvestigation of the catalysts revealed a new correlation, namely, that the catalyst activity is highly dependent on both the basicity[10] and the stoichiometry of the phosphine ligands. The effect of bidentate phosphine was the same as that previously observed, suggesting the superiority of dppf (entry 5), but the same reaction was remarkably accelerated by bulky and donating trialkylphosphines such as tri(isopropyl)phosphine (entry 11) and tri(*tert*-butyl)phosphine (entry 15) when using 1 equiv of phosphine to the rhodium metal. The use of tri(*tert*-butyl)phosphine allowed quantitative conversion even at room temperature (entry 15). Although the addition of excess of *tert*-butylphosphine dropped the yields proportionally (entries 15−17), this effect of stoichiometry was significant in small trialkylphosphines because the presence of 3 equiv of Et_3P completely stopped

Scheme 1. Addition to Aldehydes

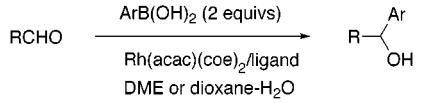

Table 1. Effect of Phosphine Ligands[a]

entry	ligand (equiv)	yield/% at 50 °C	yield/% at 80 °C
1	dppm[b] (1)		30
2	dppe[c] (1)		6
3	dppp[d] (1)		71
4	dppb[e] (1)		60
5	dppf[f] (1)	20	85
6	DPEphos[g] (1)		73
7	Xantphos[h] (1)		0
8	DBFphos[i](1)		31
9	PPh_3 (1)	33	48
10	Me_3P (1)	24	12
11	*i*-Pr_3P (1)	88	86
12	*n*-Bu_3P (1)		89
13	*i*-Bu_3P (1)	75	
14	Cy_3P[j] (1)	50	83
15	*t*-Bu_3P (1)	99 (99)[k]	79
16	*t*-Bu_3P (2)	67	77
17	*t*-Bu_3P (3)	57	

[a] A mixture of a 4-methoxybenzaldehyde (1 mmol), $PhB(OH)_2$ (2 mmol), $Rh(acac)(coe)_2$, (0.03 mmol) and a ligand (0.03−0.09 mmol) in DME/H_2O (3/2, 5 mL) was stirred for 16 h at 50 or 80 °C. [b] Bis(diphenylphosphino)methane. [c] 1,2-Bis(diphenylphosphino)ethane. [d] 1,3-Bis(diphenylphosphino)propane. [e] 1,4-Bis(diphenylphosphino)butane. [f] 1,1′-Bis(diphenylphosphino)ferrocene. [g] Bis(2-(diphenylphosphino)phenyl)ether. [h] 9,9-Dimethyl-4,6-bis(diphenylphosphino)xanthene. [i] 1,8-Bis(diphenylphosphino)dibenzofuran. [j] Tri(cyclohexyl)phosphine. [k] At room temperature for 16 h.

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Table 2. Addition of Arylboronic Acids to Aldehydes[a]

entry	$ArB(OH)_2$	aldehyde	yield[a]/% Rh(I)-$^tBu_3P$/rt	yield[b]/% Rh(I)-dppf/80 °C
1	$PhB(OH)_2$	3-$O_2NC_6H_4CHO$	94	
2		4-$O_2NC_6H_4CHO$	94	0
3		4-$F_3CC_6H_4CHO$	98	97
4		4-NCC_6H_4CHO	94	97
5		4-$MeCOC_6H_4CHO$	98	93
6		4-$MeO_2CC_6H_4CHO$	99	82
7		4-BrC_6H_4CHO	97	88
8		4-MeC_6H_4CHO	93	48 (76)[c]
9		2-MeC_6H_4CHO	88	
10		4-$MeOC_6H_4CHO$	99	83 (99)
11	4-$MeOC_6H_4B(OH)_2$	4-$MeOC_6H_4CHO$	91	
12	4-$FC_6H_4B(OH)_2$	4-$MeOC_6H_4CHO$	68	
13	4-$MeCOC_6H_4B(OH)_2$	PhCHO	98	
14		4-NCC_6H_4CHO		>1
15	2-$MeC_6H_4B(OH)_2$	4-$MeOC_6H_4CHO$	99	80
16	2,4,6-$Me_3C_6H_2B(OH)_2$	4-$F_3CC_6H_4CHO$	trace	
17	$PhB(OH)_2$	$C_5H_{11}CHO$	35 (84)[d]	69
18		*cyclo*-$C_6H_{11}CHO$	28 (90)[d]	45 (95)[c]

[a] A mixture of an aldehyde (1 mmol), $ArB(OH)_2$ (2 mmol), Rh(acac)$(coe)_2$ (0.03 mmol), and *t*-Bu_3P (0.03 mmol) in DME/H_2O (3/2, 5 mL) was stirred for 16 h at room temperature. [b] At 80 °C for 16 h in the presence of Rh(acac)$(CO)_2$/dppf (3 mol %). See ref 5. [c] At 95 °C for 16 h. [d] At 60 °C for 16 h in dioxane/H_2O (3/2, 5 mL) in the presence of Rh(acac)$(coe)_2$/*i*-Pr_3P (0.03 mmol).

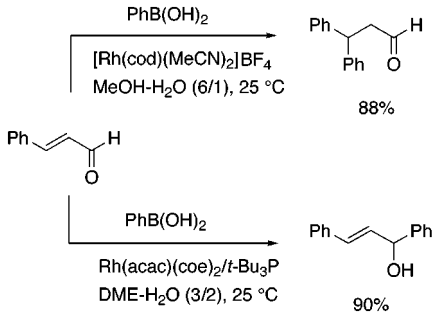
the reaction. Thus, the basicity and stoichiometry exhibited a more pronounced effect than that of bidentate ligands.

The addition of arylboronic acids to the representative aromatic and aliphatic aldehydes in the presence of Rh(acac)/*t*-Bu_3P or Rh(acac)/dppf are summarized in Table 2.

The previous reaction catalyzed by the Rh(acac)/dppf complex at 80 °C was highly sensitive to electronic effects both in aldehydes and arylboronic acids.[5] The reaction was facilitated in the presence of an electron-withdrawing group in aromatic aldehydes and a donating group in arylboronic acids. On the other hand, the addition to electron-rich aldehydes (entries 8, 17, and 18) and the arylation with electron-deficient arylboronic acids (entry 14) significantly were very slow. Moreover, no reaction was observed for 4-nitrobenzaldehyde (entry 2). However, the tri(*tert*-butyl)phosphine complex quantitatively catalyzed the reaction at room temperature for the representative aldehydes including nitrobezaldehydes (entries 1 and 2), electron-rich (entries 8−12) and electron-deficient aromatic aldehydes (entries 1−7), and electron-deficient arylboronic acid (entry 13). The additions to aliphatic aldehydes such as hexanal and cyclohexanecarbaldehyde were very slow at room temperature due to their lower electrophilicity than that of aromatic aldehydes (entries 17 and 18). The *t*-Bu_3P complex also resulted in low yields at temperature higher than 50 °C, but the *i*-Pr_3P complex that was stable at 80 °C (entry 11 in Table 1) afforded the corresponding alcohols in 84% and 90% yields, respectively (entries 17 and 18). On the other hand, no addition products were observed for acetophenone and cyclohexanone at 80 °C, suggesting high chemoselectivity for the aldehyde carbonyls.

The *t*-Bu_3P complex yielded the1,2-addition product in preference to the conjugate 1,4-addition, which was demonstrated in the addition of phenylboronic acid to cinnamaldehyde (Scheme 2). The 1,4-addition reaction catalyzed by the cationic rhodium complex in aqueous DME or dioxane gave a mixture of both isomers at 50 °C, but the same reaction proceeded smoothly at room temperature in aqueous MeOH without an accompanying a 1,2-product. The *t*-Bu_3P complex, which did not catalyze

Scheme 2. 1,4-Addition versus 1,2-Addition



the conjugate 1,4-addition, chemoselectively produced a 1,2-addition product (90%).

Many transition metal complexes catalyze the addition reactions of main group metal reagents, but the reaction mechanism has not yet been studied in detail. However, the transmetalation from a main metal reagent to a transition-metal complex has been proposed as a key step of the catalytic cycle.[11−13] The present reaction should also involve the transmetalation between the organoboronic acid and the rhodium(I) complex yielding an R−Rh(I) species, the insertion of C=O into the Rh−C bond, and finally, hydrolysis of the O−Rh(I) bond with water, as was proposed in the our previous paper (Figure 1).[5] The insertion of aldehydes into the C−Rh(I) bond has not yet been well studied, but the assumed pathway may be consistent with the related addition reactions to carbonyls; the addition of R−Rh(I) complexes (R=Me, Ph) to carbon dioxide[11] and other related additions of organostannanes[12] or organosilanes[13] to aldehydes catalyzed by a cationic rhodium complex.

The present reaction revealed an electronic effect of the functional groups both in the aldehydes and arylboronic acids, suggesting that an aryl group derived from the boronic acid nucleophilically attacks the carbonyl

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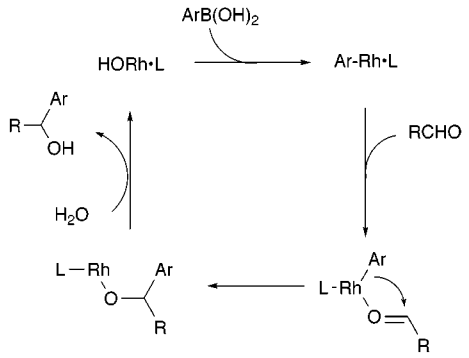

Figure 1. Proposed catalytic cycle.

carbon. The electronic effect often reduced the yields of the Rh(I)/dppf-catalyzed reaction (entries 8 and 14), whereas it was not significant in the Rh(I)/*t*-Bu_3P catalyst. Another dominant factor in both catalysts is that the dppf complex is more Lewis acidic than the *tert*-butylphosphine complex. Thus, the coordination of a nitro group to the dppf complex completely retarded the addition to nitrobenzaldehydes, though the *tert*-butylphosphine catalyst tolerates the nitro group (entries 1 and 2) and, presumably, other polar functional groups as well. There are two opposing factors in the metal catalyst both accelerating the addition to carbonyl compounds. The polarization of the C−Rh bond by the donating ligand enhances the nucleophilicity of the organic group on the rhodium metal, but the metal has to keep the Lewis acidity for coordination of the carbonyl. Thus, the coordinateively unsaturated rhodium(I) species having a limited amount of the donating ligand provides the most active catalyst since both effects can coexist at the metal center.

Experimental Section

Triphenylphosphine, tricyclohexylphosphine(PCy_3), dppm, dppe, dppp, and dppb were commercially available. PMe_3, PEt_3, P^nPr_3, P^iPr_3, P^nBu_3, P^iBu_3, and P^tBu_3 were distilled before use. Dppf was obtained by a two-step synthesis from ferrocene.[14] DPEphos, Xantphos, and DBFphos were obtained by deprotonation of the backbones with *sec*-butyllithium/TMEDA in ether; the dilithiated species are then treated with chlorodiphenylphosphine.[15] $Rh(acac)(coe)_2$ was synthesized from $[RhCl(coe)_2]_2$ and Na(acac) in toluene.[8]

General Procedure for Table 2. $Rh(acac)(coe)_2$ (0.03 mmol) and phenylboronic acid (2.0 mmol) were added to a flask containing a magnetic stirring bar. The flask was flushed with argon and then charged with DME (3 mL), (*t*-Bu_3)P (0.03 mmol), water (2 mL), and 4-methoxybenzaldehyde (1.0 mmol). The mixture was then stirred at room temperature (25−28 °C) for 16 h. The product was extracted with benzene, washed with brine, and dried over $MgSO_4$. Chromatography over silica gel gave (4-methoxyphenyl)(phenyl)methanol in 99% yield (entry 10).

1,4-Addition to *trans*-Cinnamaldehyde (Scheme 2). $[Rh(cod)(MeCN)_2]BF_4$ (0.03 mmol) and phenylboronic acid (2.0 mmol) were added to a flask containing a magnetic stirring bar, a septum inlet, and a reflux condenser. The flask was flushed with argon and then charged with MeOH (3 mL), water (0.5 mL), and *trans*-cinnamaldehyde (1.0 mmol). The mixture was then stirred for 16 h at room temperature (25−28 °C). Chromatography over silica gel (EtOAc/hexane 1/6) afforded 185 mg (88%) of the title compound as a pale yellow solid.

1,2-Addition to *trans*-Cinnamaldehyde (Scheme 2). The general procedure for Table 2 gave 189 mg (90%) of the title compound as a clear oil.

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Supporting Information Available: The procedures for Tables 1 and 2 and Scheme 2 and spectral analyses of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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