

# *t*-Bu-Amphos–RhCl<sub>3</sub>·3H<sub>2</sub>O: a highly recyclable catalyst system for the cross-coupling of aldehydes and aryl- and alkenylboronic acids in aqueous solvents†

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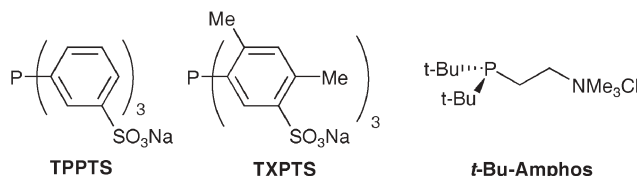
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The combination of *t*-Bu-Amphos and RhCl<sub>3</sub>·3H<sub>2</sub>O gave the first highly recyclable catalyst for the coupling of aryl- and vinylboronic acids with aldehydes in aqueous solvents.

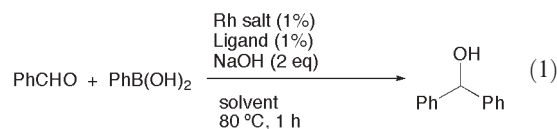
Addition of carbon nucleophiles to carbonyl compounds, such as in Grignard–Barbier reactions, is a classic method for carbon–carbon bond formation. Rhodium-catalyzed addition of air- and moisture-stable organoboron or organotin reagents offers a more functional group tolerant method than the traditional Grignard–Barbier reagents.<sup>1</sup> In addition, by use of chiral ligands, modest enantioselectivities have been achieved with this methodology.<sup>2–4</sup> Oi *et al.*<sup>5</sup> and Miyaura *et al.*<sup>2</sup> initially reported the rhodium-catalyzed addition of arylstannanes and arylboronic acids to aldehydes, respectively. Ueda and Miyaura<sup>6</sup> subsequently showed that sterically demanding alkylphosphines, such as *t*-Bu<sub>3</sub>P gave more active catalysts than the chelating arylphosphines used in his original report. Strongly  $\sigma$ -donating *N*-heterocyclic carbene ligands have also been shown to be highly effective in these coupling reactions.<sup>7,8</sup>



We have recently reported the use of sterically demanding, water-soluble alkylphosphines, such as *t*-Bu-Amphos, to give active and recyclable catalysts for aqueous-phase palladium-catalyzed cross-coupling reactions.<sup>9,10</sup> While aqueous–organic solvent systems are commonly used in the Rh-catalyzed arylation of aldehydes, the use of hydrophobic ligands precludes retention of the catalyst in the aqueous-phase. By using a hydrophilic ligand, we envisioned that the rhodium catalyst would be retained in the aqueous-phase of an aqueous–organic biphasic system, allowing the catalyst to be easily recovered and potentially recycled. Li *et al.*<sup>11,12</sup> have reported ligand-free rhodium-catalyzed additions of organoboron and tin reagents to aldehydes in water, although the recyclability of this catalyst was not described. Rhodium

sources in combination with hydrophilic phosphines, such as TPPTS and *t*-Bu-Amphos, have been shown to promote the addition of arylboronic acids to activated alkenes in aqueous solvents.<sup>13–17</sup> To the best of our knowledge, there are no reports of the use of hydrophilic catalysts for the addition of organoboron reagents to aldehydes in aqueous solvents.

The coupling of benzaldehyde and phenylboronic acid in 1 : 1 water–acetonitrile at 80 °C was chosen as the initial model reaction on which to optimize the catalytic system (eqn (1), Table 1). Initial scouting reactions indicated that sodium hydroxide was required for the reaction to proceed and that 80 °C was the optimal temperature for acceptable reaction rates. Using these conditions as a starting point, the effects of changing the rhodium source, ligand, and solvent system were explored. Catalysts derived from sulfonated arylphosphines (TPPTS and TXPTS) were inactive under these conditions (Table 1, entries 2 and 3). Use of 1 : 1 toluene–water gave the same yield (84%) as 1 : 1 water–acetonitrile, while use of water as the only solvent gave slightly higher yields (90%). RhCl<sub>3</sub>·3H<sub>2</sub>O, [RhCl(cod)]<sub>2</sub>, and Rh(acac)(coe)<sub>2</sub> (coe = cyclooctene) all gave nearly identical yields when used as the rhodium source in coupling reactions carried out in water (88–90%, Table 1, entries 5–7). Commercially available and air-stable RhCl<sub>3</sub>·3H<sub>2</sub>O was chosen as the most convenient catalyst precursor for further study.



Using the *t*-Bu-Amphos–RhCl<sub>3</sub>·3H<sub>2</sub>O catalyst system, phenylations of a variety of aldehydes were carried out in 1 : 1 water–acetonitrile at 80 °C (Table 2). Benzhydrol was obtained from benzaldehyde in 82% isolated yield under these conditions, while

**Table 1** Catalyst optimization studies<sup>a</sup>

Entry	Rh salt	Ligand	Solvent	Yield (%) <sup>b</sup>
1	RhCl <sub>3</sub> ·3H <sub>2</sub> O	<i>t</i> -Bu-Amphos	CH <sub>3</sub> CN–H <sub>2</sub> O <sup>c</sup>	85
2	RhCl <sub>3</sub> ·3H <sub>2</sub> O	TPPTS	CH <sub>3</sub> CN–H <sub>2</sub> O <sup>c</sup>	0
3	RhCl <sub>3</sub> ·3H <sub>2</sub> O	TXPTS	CH <sub>3</sub> CN–H <sub>2</sub> O <sup>c</sup>	0
4	RhCl <sub>3</sub> ·3H <sub>2</sub> O	<i>t</i> -Bu-Amphos	Toluene–H <sub>2</sub> O <sup>d</sup>	84
5	RhCl <sub>3</sub> ·3H <sub>2</sub> O	<i>t</i> -Bu-Amphos	H <sub>2</sub> O	90
6	[RhCl(cod)] <sub>2</sub>	<i>t</i> -Bu-Amphos	H <sub>2</sub> O	88
7	Rh(acac)(coe) <sub>2</sub>	<i>t</i> -Bu-Amphos	H <sub>2</sub> O	90

<sup>a</sup> Benzaldehyde (1 equiv.), phenylboronic acid (1.5 equiv.), NaOH (2 equiv.), Rh salt (0.01 equiv.), ligand (0.01 equiv.), 1.5 mL solvent, 80 °C, 1 h. <sup>b</sup> GC yield. <sup>c</sup> 1 : 1 CH<sub>3</sub>CN–H<sub>2</sub>O. <sup>d</sup> 1 : 1 toluene–H<sub>2</sub>O.

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**Table 2** Phenylboronic acid addition to aldehydes

$\text{RCHO} + \text{PhB(OH)}_2 \xrightarrow[\substack{1:1 \text{ CH}_3\text{CN}/\text{H}_2\text{O} \\ 80^\circ\text{C}, 2 \text{ h}}]{\substack{\text{RhCl}_3 \cdot 3\text{H}_2\text{O} (1\%) \\ t\text{-Bu-Amphos} (1\%) \\ \text{NaOH} (2 \text{ eq})}} \text{R-CH(OH)-Ph}$			
Entry	Aldehyde	Product	Yield (%) <sup>a</sup>
1	PhCHO		82 78 <sup>b</sup>
2	<i>p</i> -CN-C <sub>6</sub> H <sub>4</sub> CHO		86
3	<i>p</i> -Br-C <sub>6</sub> H <sub>4</sub> CHO		77
4	<i>p</i> -F-C <sub>6</sub> H <sub>4</sub> CHO		78
5	<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> CHO		59
6	<i>o</i> -Me-C <sub>6</sub> H <sub>4</sub> CHO		78
7	C <sub>8</sub> H <sub>17</sub> CHO		50
8	<i>c</i> -C <sub>6</sub> H <sub>11</sub> CHO		52
9	<i>t</i> -BuCHO		0

<sup>a</sup> 1 mol% RhCl<sub>3</sub>·3H<sub>2</sub>O–*t*-Bu-Amphos, 1 : 1 H<sub>2</sub>O–CH<sub>3</sub>CN, 80 °C, 2 h. Average isolated yield of two runs. <sup>b</sup> Reaction run in water.

the same reaction in water gave a 78% yield (Table 2, entry 1). Benzaldehyde derivatives with electron withdrawing groups gave good yields of benzhydrol derivatives (Table 2, entries 2–4). In contrast, incorporation of an electron releasing group gave lower yields (Table 2, entry 5), even with long reaction times. Incorporation of an *ortho*-methyl substituent on the aldehyde had no effect on the reaction yield. Heptaldehyde and cyclohexanecarbaldehyde gave modest yields of coupled product, while pivaldehyde gave no conversion (Table 2, entries 7–9). The lower electrophilicity of the aliphatic aldehydes likely accounted for the lower yields obtained with these substrates.

A contrasting electronic effect was seen when substituted arylboronic acids were used (Table 3). Electron rich 4-methoxyphenylboronic acid gave good yields of coupled product (Table 3, entry 1), while electron deficient arylboronic acids gave low to

moderate yields (23–55%) of coupling products (Table 3, entries 3–5). Longer reaction times gave only marginally higher yields in these reactions. An optimized system with an electron deficient benzaldehyde derivative and an electron rich arylboronic acid gave a 90% yield of the benzhydrol product. 2-Tolylboronic acid gave similar yields to sterically unhindered arylboronic acids (Table 3, entry 6). *E*-1-Octenylboronic acid also gave good yields in couplings with benzaldehyde derivatives to give *E*-1-aryl-2-alken-1-ols (Table 3, entries 7–9). An attempt to alkylate benzaldehyde with 1-butylboronic acid was unsuccessful, however.

Although some limitations were encountered in exploring the substrate scope, the complementary requirements for the aldehyde and boronic acid allow most desired products to be obtained in good yields. For example, the use of 4-cyanophenylboronic acid and benzaldehyde gave a 23% yield of 4-cyanobenzhydrol, while the same compound could be made in 86% yield by placing the electron withdrawing group on the aldehyde electrophile. Similarly, 1-aryl-1-alkanols could not be prepared from benzaldehyde and an alkylboronic acid, but could be prepared in moderate yield by using an arylboronic acid and an aliphatic aldehyde.

One important advantage to using a hydrophilic catalyst in an aqueous-biphasic solvent mixture is the potential to easily recover and recycle the aqueous catalyst containing phase. The recyclability of the *t*-Bu-Amphos–Rh catalyst system was explored in the model coupling of benzaldehyde and phenylboronic acid. The initial reaction was run using 2 mol% RhCl<sub>3</sub>·3H<sub>2</sub>O–*t*-Bu-Amphos in water at 80 °C for 1 h. Upon completion, the reaction mixture was extracted with deoxygenated ethyl acetate. Analysis of the organic phase by GC indicated that benzhydrol was produced in 79% yield (Table 4). The aqueous phase containing the catalyst was transferred to a new vial under nitrogen containing fresh substrates and base. The vial was then heated at 80 °C for 1 h and the product recovered as before. This process was repeated for a total of 9 reaction cycles. As the recycling study progressed, salts began to precipitate from the aqueous phase. After completion of the sixth cycle, the aqueous phase was allowed to stand overnight. The aqueous supernatant was then removed from the precipitated salts and used for cycles 7–9.

**Table 3** Coupling of aldehydes and boronic acids

$\text{RCHO} + \text{R'B(OH)}_2 \xrightarrow[\substack{1:1 \text{ CH}_3\text{CN}/\text{H}_2\text{O} \\ 80^\circ\text{C}, 2 \text{ h}}]{\substack{\text{RhCl}_3 \cdot 3\text{H}_2\text{O} (1\%) \\ t\text{-Bu-Amphos} (1\%) \\ \text{NaOH} (2 \text{ eq})}} \text{R-CH(OH)-R'}$			
Entry	RCHO	R'B(OH) <sub>2</sub>	Yield (%) <sup>a</sup>
1	PhCHO	<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	79
2	<i>p</i> -CN-C <sub>6</sub> H <sub>5</sub> CHO	<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	90
3	PhCHO	<i>p</i> -F-C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	55
4	PhCHO	<i>p</i> -NC-C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	23
5	PhCHO	<i>p</i> -HO <sub>2</sub> C-C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	28
6	PhCHO	<i>o</i> -Me-C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	86
7	PhCHO	( <i>E</i> -1-octenyl)B(OH) <sub>2</sub>	84
8	<i>p</i> -CN-C <sub>6</sub> H <sub>5</sub> CHO	( <i>E</i> -1-octenyl)B(OH) <sub>2</sub>	71
9	<i>o</i> -Me-C <sub>6</sub> H <sub>5</sub> CHO	( <i>E</i> -1-octenyl)B(OH) <sub>2</sub>	73
10	PhCHO	<i>n</i> -C <sub>4</sub> H <sub>9</sub> B(OH) <sub>2</sub>	0

<sup>a</sup> 1 mol% RhCl<sub>3</sub>·3H<sub>2</sub>O–*t*-Bu-Amphos, 1 : 1 H<sub>2</sub>O–CH<sub>3</sub>CN, 80 °C, 2 h. Average isolated yield of two runs.

**Table 4** Recycling of the *t*-Bu-Amphos–RhCl<sub>3</sub> catalyst system<sup>a</sup>

Cycle	Yield (%) <sup>b</sup>	Cycle	Yield (%) <sup>b</sup>
1	79	6	90
2	83	7	86
3	90	8	74
4	85	9	76
5	90		

<sup>a</sup> Coupling of benzaldehyde (0.3 mmol) and phenylboronic acid (0.33 mmol), 2 mol% *t*-Bu-Amphos–RhCl<sub>3</sub>, water (1.5 mL), 80 °C, 1 h. Cycles 2–9 used the aqueous catalyst solution from the previous cycle. <sup>b</sup> GC yield of benzhydrol obtained by ethyl acetate extraction of the reaction mixture.

The catalyst proved to be highly stable in the recycling study, during which the benzhydrol yield ranged from 74 to 90% with an average yield of 84%. The yield in the initial run was slightly lower than we typically see in single runs, possibly due to incomplete extraction of the benzhydrol product. After the first cycle, the yields varied from run to run, but remained between 83 and 90%. Notably, the filtration after the sixth reaction cycle did not appear to have a significant effect on catalyst activity. Only in the 8th and 9th cycles do the yields drop slightly. Even with this drop in yield, the catalyst appears to retain a significant level of activity. To the best of our knowledge, this work represents the first report of a recyclable catalyst for the addition of organometallic reagents to aldehydes. Nine cycles with a single catalyst charge is the highest number of cycles that we are aware of in a Rh-catalyzed coupling reaction.<sup>16,17</sup>

The fact that the catalyst could be used for nine reaction cycles at 80 °C shows that the active species is robust. Furthermore, the active catalyst species must be soluble in water, since decantation from precipitated salts after the 6th cycle had little effect on the yield of the subsequent cycle. Therefore the involvement of a heterogeneous rhodium catalyst, either as the active species or a reservoir for soluble Rh nanoparticles, can likely be excluded in this system. Ueda and Miyaura<sup>6</sup> have proposed that the active species in his *t*-Bu<sub>3</sub>P–Rh(I) catalyst system is a coordinatively

unsaturated LRh(OH) complex. The *t*-Bu-Amphos–RhCl<sub>3</sub> pre-catalyst could give this type of active species upon reduction of Rh(III) to Rh(I) with phenylboronic acid. We are currently investigating the nature of the active species in this system.

In conclusion we have shown that the *t*-Bu-Amphos–RhCl<sub>3</sub>·3H<sub>2</sub>O catalyst system provides an effective catalyst for the addition of aryl- and vinylboronic acids to both aryl and aliphatic aldehydes in aqueous solvents. Significantly the catalyst could be used for 9 reaction cycles with little change in the yield of benzhydrol.

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