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New studies of Rh-catalyzed addition of boronic acids under basic conditions in aqueous medium

Rémi Amengual, Véronique Michelet* and Jean-Pierre Genêt*

Laboratoire de Synthèse Sélective Organique et Produits Naturels, E.N.S.C.P., UMR 7573, 11 rue P. et M. Curie, F-75231 Paris Cedex 05, France

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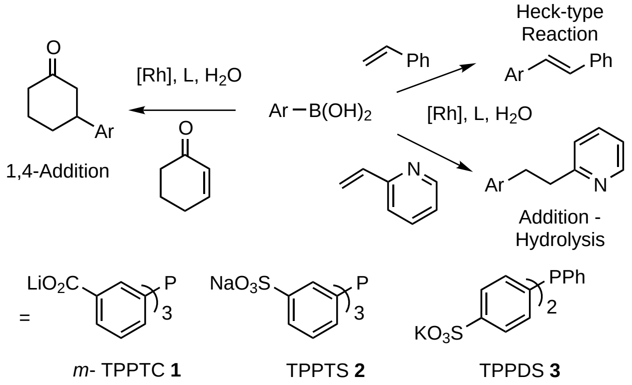
Abstract—Rh-catalyzed C–C bond formation in neat water under basic conditions has been efficiently performed. The addition of various boronic acids to styrene, 2-vinylpyridine, and cyclic α,β-unsaturated ketones has been realized with high selectivity and yield. We have shown that *m*-TPPTC (tris(*m*-carboxyphenyl)phosphane trilithium salt) exhibited a higher reactivity compared to TPPTS. These couplings could also be conducted very efficiently under basic and phosphaneless conditions to give functionalized aryl derivatives. The benefits of the additional anionic ligand *m*-TPPTC lied in the successful recycling experiments of 1,4-addition of phenylboronic acid to cyclohexenone, with no loss of the water-soluble catalyst. © 2002 Elsevier Science Ltd. All rights reserved.

Carbon–carbon bond formation is fundamentally important in organic synthesis. Recent years witnessed tremendous growth in a number of reactions and reagents for C–C bond formation. Among them, the transition metal-catalyzed reactions and specifically homogeneous catalysis have given a considerable impetus to the progress of the area of organometallic, organic and industrial chemistry.[1] The development of efficient environmentally safe systems has given the ability to combine the high activity and selectivity of the catalyst with the easier product separation and possible catalyst recycling.[2] We have been engaged for a long time in a program devoted to reactions in organoaqueous media using TPPTS ligand (tris(*m*-sulfonatophenyl)phosphane trisodium salt), such as palladium-catalyzed reactions,[3,4] nickel-catalyzed cross-couplings[5] and palladium, rhodium or nickel-catalyzed ene-reaction.[6]

New C–C bond formations have recently been reported in water using rhodium catalysts.[7] The addition of boronic acids to either styrene derivatives[7a] or α,β-unsaturated ketones[7c] resulted in low yields using Rh/TPPTS system (Scheme 1). We have reported very recently the easy preparation of the new highly water-soluble ligand *m*-TPPTC **1** (tris(*m*-carboxyphenyl)phosphane trilithium salt).[8] Preliminary studies showed that, the reactivity of *m*-TPPTC was similar to TPPTS in palladium-catalyzed reactions, but no reaction mediated by rhodium was tested so far with this ligand. We wish therefore to describe herein the applications of our new hydrophilic ligand **1** in rhodium-catalyzed reactions.

We first turned our attention to the coupling of boronic acids with either styrene or 2-vinylpyridine (Scheme 1). Boronic acids may be engaged in Rh-catalyzed reactions via a Heck-type reaction (addition–elimination) or via an addition–hydrolysis. In the literature, the use of the disulfonated water-soluble ligand TPPDS **3** (bis(*p*-sulfonatophenyl)phenylphosphane dipotassium salt)[9] associated with a surfactant (sodium dodecyl sulfate



Scheme 1.

Keywords: water-soluble ligand; boronic acids; α,β-unsaturated ketones; styrene derivatives; recyclable rhodium/*m*-TPPTC system.

* Corresponding authors. E-mail: michelet@ext.jussieu.fr; genet@ext.jussieu.fr

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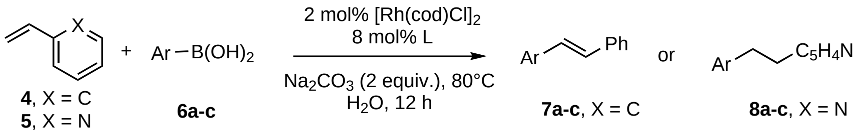
SDS) appeared to be necessary for the couplings in water.[7a] As we experimentally observed a surfactant effect for the *m*-TPPTC ligand, we conducted the reaction directly in water without SDS (Table 1). Indeed, the coupling of phenylboronic acid with styrene using 2 mol% of rhodium dimer, 8 mol% of *m*-TPPTC in neat water at 80°C gave stilbene **7a** with 79% yield (entry 1). The reaction was very clean and after an easy work up that consists in two extractions and a filtration of the organic phase on a silica gel pad, stilbene was isolated in high purity (gas chromatography).[10] The same reaction conducted with TPPTS ligand was very sluggish and gave only 31% of the desired compound (entry 2). In the case of 4-bromophenylboronic acid **6b** (entry 4), the reaction occurred with an excellent chemoselectivity. Electro-donating group was also tolerated as illustrated by the addition of 4-methoxyphenylboronic acid **6c** (entry 7). Our system with *m*-TPPTC **1** was therefore extremely efficient without the use of SDS. Stilbene derivatives **7b** and **7c** were isolated with 96 and 71% yield, respectively (entries 4, 7). In contrary, TPPTS **2** ligand gave poor results in these reactions (entries 5, 8). The catalytic cycle of either C–C bond couplings involves a transmetallation between $ArB(OH)_2$ and the Rh catalyst, and insertion of the alkene and finally a Rh–H elimination of the rhodium intermediate. The higher efficiency of *m*-TPPTC compared to TPPTS may be then explained in terms of basicity of the phosphanes that would favor the transmetallation step.[11] The addition of boronic acids on 2-vinylpyridine was also efficiently performed using *m*-TPPTC ligand. The heteroaryl compounds were respectively isolated with 67 and 66% yield (entries 10, 12). Suspected that the reaction might be catalyzed only by Rh(I),[7c] we performed the couplings of boronic acids on styrene derivatives **4** and **5** without additional phosphane ligand. Indeed, the boron partners still reacted very smoothly in the standard basic conditions. Stilbene derivatives were obtained with 84–99% isolated yields (entries 3, 6, 9). In the case of the addition–hydrolysis pathway, the corresponding functionalized aryl derivatives could also be isolated in good yield (entries 11, 13).

Then, we turned our attention to the 1,4-addition of boronic acids to α,β-unsaturated ketones.[12,13] Encouraged by the previous good results in neat water, we decided to use 2 mol% of $[Rh(cod)Cl]_2$, 8 mol% ligand, 2 equiv. of Na_2CO_3 at 80°C. As documented in Table 2, the addition of phenylboronic acid **6a** to cyclohexenone **9** led very efficiently to the arylated cyclohexanone with 99% isolated yield (entry 1). The reaction was much faster than the one with 2-vinylpyridine, because α,β-unsaturated ketones are excellent Michael acceptors. Under the same conditions, the use of TPPTS ligand gave this time an excellent result too: the reaction was complete within 1 h at 80°C in neat water (entry 2). Without additional phosphane ligand, the addition of **6a** was much faster (0.25 h versus 1 h) and the desired 1,4-adduct **12a** was isolated with 99% yield (entry 3). We then checked the generality of this phosphaneless reaction under standard basic conditions. Either electro-donating boronic acid **6c** (entry 4) or electro-withdrawing boronic acid **6d** (entry 5) could react in short reaction time leading to 99% isolated compounds.

The highly hindered boronic acid **6e** could also be a good partner (entry 6). Other enones like cyclopentenone **10** or cycloheptenone **11** (entries 7, 8) afforded the corresponding adducts **13a** and **14c** with quantitative yield. All compounds were characterized by NMR and GC/mass spectroscopy. The addition of boronic acids on α,β-unsaturated ketones was therefore efficiently realized in short time at 80°C with or without additional ligand, in neat water and in the presence of a base. It has to be noticed that the presence of a base accelerates the reaction compared to previous reports.

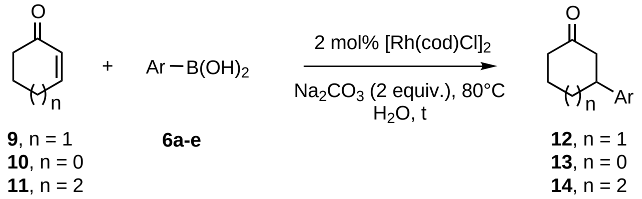
Table 1. Rh-catalyzed addition of boronic acids to styrene derivatives



Entry	Styrene	Boronic acid	Ligand	Product	Yield (%)[a]
1	**4**	$PhB(OH)_2$ **6a**	*m*-TPPTC **1**	**7a**	79
2	**4**	$PhB(OH)_2$ **6a**	TPPTS **2**	**7a**	31
3	**4**	$PhB(OH)_2$ **6a**	/	**7a**	99
4	**4**	$4\text{-BrC}_6H_4B(OH)_2$ **6b**	*m*-TPPTC **1**	**7b**	96
5	**4**	$4\text{-BrC}_6H_4B(OH)_2$ **6b**	TPPTS **2**	**7b**	24
6	**4**	$4\text{-BrC}_6H_4B(OH)_2$ **6b**	/	**7b**	99
7	**4**	$4\text{-MeO-C}_6H_4B(OH)_2$ **6c**	*m*-TPPTC **1**	**7c**	71
8	**4**	$4\text{-MeO-C}_6H_4B(OH)_2$ **6c**	TPPTS **2**	**7c**	32
9	**4**	$4\text{-MeO-C}_6H_4B(OH)_2$ **6c**	/	**7c**	84
10	**5**	$PhB(OH)_2$ **6a**	*m*-TPPTC **1**	**8a**	67
11	**5**	$PhB(OH)_2$ **6a**	/	**8a**	80
12	**5**	$4\text{-MeO-C}_6H_4B(OH)_2$ **6c**	*m*-TPPTC **1**	**8c**	66
13	**5**	$4\text{-MeO-C}_6H_4B(OH)_2$ **6c**	/	**8c**	77

[a] Isolated yield.

Table 2. Rh-catalyzed addition of boronic acids to enones



Entry	Enone	Boronic acid	Ligand	Product	Time (h)	Yield (%)[a]
1	**9**	$PhB(OH)_2$ **6a**	*m*-TPPTC **1**	**12a**	1	99
2	**9**	$PhB(OH)_2$ **6a**	TPPTS **2**	**12a**	1	99
3	**9**	$PhB(OH)_2$ **6a**	/	**12a**	0.25	99
4	**9**	4-MeO-$C_6H_4B(OH)_2$ **6c**	/	**12c**	2	99
5	**9**	4-CF_3-$C_6H_4B(OH)_2$ **6d**	/	**12d**	1	99
6	**9**	2,6-Me_2-$C_6H_3B(OH)_2$ **6e**	/	**12e**	3	99
7	**10**	$PhB(OH)_2$ **6a**	/	**13a**	1	99
8	**11**	4-MeO-$C_6H_4B(OH)_2$ **6c**	/	**14c**	1	99

[a] Isolated yield.

A major advantage of water-soluble phosphane lie in the recycling possibility of the catalyst, that is therefore preserved in water. Thus, we envisaged improving our catalyst system Rh(I)/*m*-TPPTC by recycle experiments. We have conducted the 1,4-addition of phenylboronic acid to cyclohexenone using 0.5 mol% $[Rh(cod)Cl]_2$, 1 mol% *m*-TPPTC **1** under our standard basic conditions. As shown in Fig. 1, we were pleased to find that the benefits of the water-soluble ligand **1** lied in the successful recycling of the expensive rhodium. Indeed, after completion of the reaction, the water phase (containing the catalyst and the product) was extracted two times with cyclohexane and reloaded with substrates. The reaction time was still very short for each recycling (between 1 and 1.5 h). The arylated ketone was isolated with 87–100% yield and with excellent purity (98%). It is noteworthy that during the continuous recycle experiments, no deposition of rhodium metal on the glass was observed.

In conclusion, Rh-catalyzed C–C bond formation in neat water under basic conditions has been efficiently performed. The addition of various boronic acids to styrene gave, via a Heck-type reaction, stilbene derivatives. Poor Michael acceptor such as 2-vinylpyridine selectively underwent 1,4-addition of an aryl group. We have shown that, in those cases, the use of an additional phosphane was not necessary. Nevertheless, a better reactivity was observed when using *m*-TPPTC compared to TPPTS, presumably due to a difference of basicity of the ligands.[11] We have also realized Rh-catalyzed couplings on α,β-unsaturated ketones under basic conditions with or without additional water-soluble ligand, which may be a drawback for asymmetric catalysis.[12,13] We have shown that the water-soluble Rh/*m*-TPPTC could be easily recycled for the first time in water with no loss of the selectivity. We are currently looking for optimized conditions to perform asymmetric C–C bond formation using chiral water-soluble ligands.

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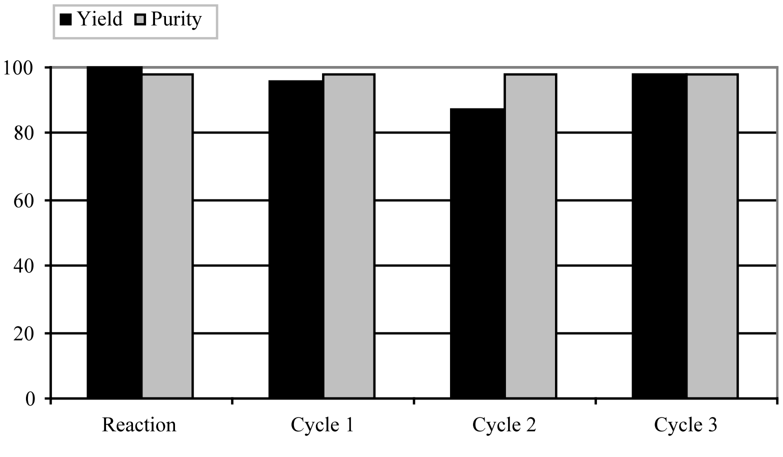

Figure 1. Addition of phenylboronic acid to cyclohexenone.

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10. Typical procedure: To a mixture of degassed $[Rh(cod)Cl]_2$ (4.3 mg, 2 mol%) and *m*-TPPTC (14.5 mg, 8 mol%) at room temperature was successively added water (2.2 mL), phenylboronic acid (133 mg, 1.09 mmol), Na_2CO_3 (92 mg, 0.86) and styrene (50 μL, 0.43 mmol). The heterogeneous mixture was heated at 80°C until completion of the reaction (gas chromatography) and then cooled to room temperature, extracted with ethyl acetate (two times) and dichloromethane (two times). The combined organic layers were filtered on a short pad of silica gel and evaporated under reduced pressure. A white solid (60 mg, 79%) was obtained. No further purification was necessary. The purity (>98%) was checked by NMR and GC–MS analyses.
11. The higher basicity of *m*-TPPTC compared to TPPTS was recently established in our laboratory (E. Genin, D.E.A. Multinational de Chimie Moléculaire de l'Ecole Polytechnique).
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