The rhodium-catalysed 1,2-addition of arylboronic acids to aldehydes and ketones with sulfonated S-Phos

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ABSTRACT

The rhodium-catalysed 1,2-addition of arylboronic acids to aryl aldehydes has been accomplished in high yield using sulfonated S-Phos, a water-soluble biaryl phosphine ligand which allows for catalyst recycling. The catalytic protocol has also been successful in the challenging arylation of ketones.

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The synthesis of alcohols by the insertion of aldehydes into the metal–carbon bonds of rhodium complexes has emerged as a useful method for organic synthesis.[1] Miyaura and co-workers first described the efficient addition of arylboronic acids to aldehydes in aqueous solution employing phosphine complexes having a large P-Rh-P angle and also with bulky and donating trialkyl phosphines.[2] A number of other ligands have been used to prepare rhodium complexes with excellent activity for this important synthetic process.[3] The use of enantiopure ligands has afforded good levels of enantioselectivity.[2a,4] An appealing advance in this area is the report of enantioenriched secondary and tertiary alkylboron derivatives adding to aldehydes with complete stereoretention in the presence of an appropriate rhodium complex.[5] The rhodium-catalysed addition of arylboronic acids to aldehydes is noted to tolerate aqueous reaction conditions which can offer distinct benefits in terms of reactivity and the prospect of catalyst recycling.[6] In this context, Shaughnessy and co-workers reported that a combination of t-Bu-Amphos 8 and RhCl₃·3H₂O provides a recyclable catalyst for the coupling of aryl- and vinylboronic acids with aldehydes in aqueous solvents.[7] In this Letter, we report the application of a sulfonated biaryl phosphine ligand in rhodium-catalysed additions of arylboronic acids to aldehydes and, remarkably, ketones. S-Phos 5 is a key member of a family of rationally designed biaryl phosphine ligands introduced by Buchwald and co-workers that have shown immense potential in the Suzuki–Miyaura couplings of challenging substrates.[8] The ready availability of a sulfonated S-Phos 6 inspired us to investigate the possibility of developing a robust and recyclable catalyst system for the arylation of aldehydes.[9]

Initial results were immediately promising, with p-tolualdehyde 1 being completely converted into the diaryl-carbinol product 3 (isolated in 86% yield) in two hours at 80 °C (Scheme 1).

Extraction of the organic product using diethyl ether and subsequent addition of more reagents to recycle the catalyst species yielded continued conversion (Table 1, entries 1–3). Also the room temperature activity of the catalyst suggested high activity (Table 1, entry 4). However the use of an alternative phosphine, TPPMS-Li (7), containing the easily prepared backbone common to many industrially applied water-soluble phosphine ligands,[10] showed significantly lower ability to turnover the reaction in recycling experiments (Table 1, entries 5–7). These results prompted us to attempt additions to related ketone substrates, progress in this area is not so advanced due to the lower reactivity in part due to the increased steric demands imposed in these systems.[11] So far, only highly activated ketones have been shown to undergo the 1,2-addition reaction with arylboronic acids using transition metal catalysts.[12] These typically include electronically activated sub-
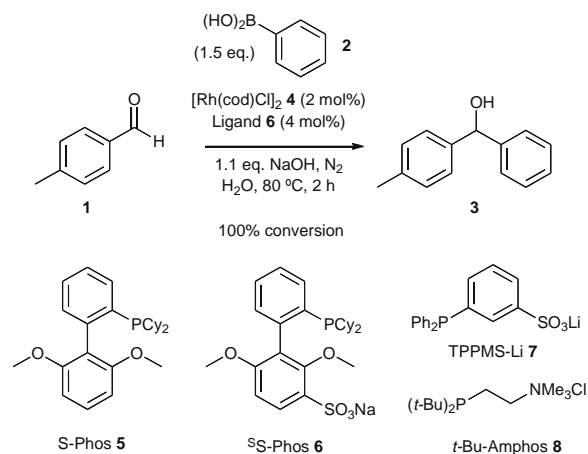
Scheme 1.

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Table 1
Activity and recycling of rhodium complexes with water-soluble ligands
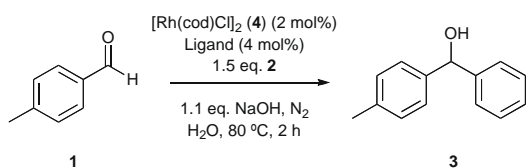
Entry	Ligand	% Conv.[a]
1	6	100
2[b]	6	81
3[c]	6	66
4[d]	6	100
5[b]	7	46
6[c]	7	Trace
7	7	83

All reactions performed on 1.0 mmol of aldehyde in water (1.5 ml).
[a] As determined by ^{1}H NMR spectroscopy.
[b] Second run. Recycle via extraction of organic components, followed by the addition of a further 1.0 equiv of aldehyde and 1.5 equiv of boronic acid per cycle to the aqueous catalyst and designated ligand.
[c] Third run.
[d] Reaction performed at rt for 48 h.

strates such as trifluoromethylketones,[13] and various 1,2-dicarbonyl derivatives.[14] The reaction has also been shown to work with tethered ketone/boronic acid systems in an intramolecular fashion.[15]

We therefore selected p-nitroacetophenone (9) and p-methoxyphenylboronic acid (10) to use in a more challenging addition. The initial conditions gave an encouraging 41% conversion as determined by ^{1}H NMR (Table 2, entry 1). Purification by column chromatography afforded diaryl-methylcarbinol 11 in a 39% yield. With this convenient model system we then proceeded to further investigate the reaction parameters. A brief base screen showed metal hydroxides to be most effective (Table 2, entries 3 and 11), and a hydroxy-rhodium species or appropriate precatalyst was found to be essential (Table 2, entries 3–8). This is consistent with literature precedent, where the active species for transmetallation

Table 2
Initial results for the ketone arylation
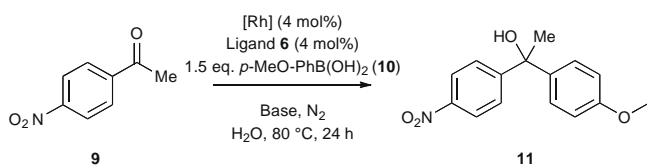
Entry	Catalyst	Base[a]	% Conv.[b]
1	[Rh(cod)Cl]$_2$ (4)	NaOH	41 (39)[c]
2	4	NaOH	43 (29)[d]
3	4	NaOH	40
4	(None)	NaOH	0
5	RhCl$_3$·3H$_2$O	NaOH	0
6	[Rh(acac)(C$_2$H$_4$)$_2$]$_2$	NaOH	0
7	Rh$_2$(tfa)$_4$	NaOH	0
8	[Rh(cod)OH]$_2$	NaOH	40
9	4	K$_2$CO$_3$	17
10	4	NEt$_3$	30
11	4	KOH	41
12	4	None	21

All reactions performed on 0.125 mmol of ketone in water (1.5 ml), except entries 1 and 2 where 1.0 mmol of ketone was used in water (3.0 ml).
[a] 1.1 equiv of base.
[b] As determined by ^{1}H NMR spectroscopy, isolated yields in parentheses.
[c] Reaction time of 2 h.
[d] Without ligand, reaction time extended to 48 h; purification was complicated by product colouration suggesting metal contamination.

is often a hydroxy-rhodium intermediate, which can be produced in situ using aqueous alkali-metal hydroxides and a suitable precatalyst.[16] The use of smaller amounts of base also retarded conversion, probably due to the presence of increasing amounts of boric acid as by-product, which results in an unfavourable environment for catalyst turnover.[17]

Our attempts to increase conversion employing a 1:1 ratio of water and co-solvent to improve mixing were unsuccessful (Table 3, entries 2–5). The use of polar aprotic solvents gave poor results, possibly due to complexation with the metal centre and subsequent deactivation. The only improvement came with increasing the concentration of the reaction mixture in water, this resulted in a useful 51% conversion (Table 3, entry 8). Unfortunately, varying the temperature at this higher concentration showed no further improvement.

Using this optimised set of conditions we revisited the aldehyde substrates to improve the catalyst recycling. Importantly, we noted that the addition of a portion of base for each recycle of the catalyst allowed high activity to be maintained over five reactions of 1 (Table 4). This indicated that the drop-off in catalytic activity we observed previously (Table 1, entries 1–3) was not due to degradation of the catalytically active species during the recycling

Table 3
Effect of co-solvent and temperature on ketone arylation
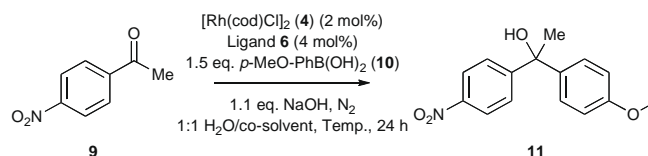
Entry	Co-solvent	Temp (°C)	% Conv.[a]
1	(H$_2$O)	80	40
2	MeCN	80	5
3	DMSO	80	8
4	1,4-Dioxane	80	9
5	IPA	80	30
6	None	40	32
7	None	60	39
8	None	80	51
9	None	100	46

All reactions performed on 0.125 mmol of ketone in water (0.75 ml) with co-solvent (0.75 ml). Where no co-solvent was used the total volume of water remained at 0.75 ml.
[a] As determined by ^{1}H NMR spectroscopy.

Table 4
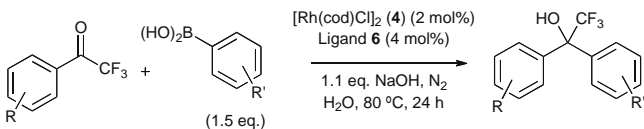Optimised aldehyde arylations and catalyst recycling
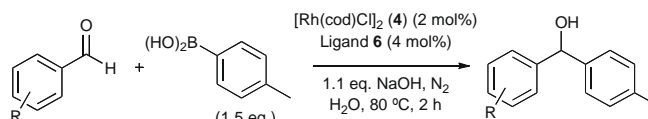
Entry	Cycle	R	% Conv.[a]
1	–	p-F	100 (91)
2	–	p-OMe	97[b]
3	1	p-Me	>99 (96)
4	2[c]	p-Me	>99
5	3[c]	p-Me	>99
6	4[c]	p-Me	>99
7	5[c]	p-Me	>99 (97)

All reactions performed on 1.0 mmol of aldehyde in water (1.5 ml).
[a] As determined by ^{1}H NMR spectroscopy, isolated yield in parentheses.
[b] Degradation, primarily to the diaryl ketone, occurred during purification.
[c] 1.0 equiv of aldehyde, 1.5 equiv of boronic acid and 1.1 equiv of base added per cycle. Products removed after cooling via extraction with diethyl ether.

Table 5
Trifluoromethyl ketone arylations

All reactions performed on 1.0 mmol of ketone in water (1.5 ml).
  a Isolated yield after column chromatography.
  b The starting ketone was recovered quantitatively.

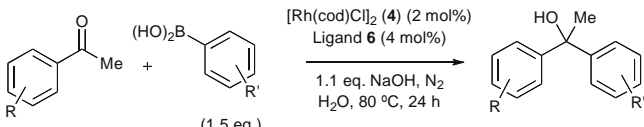| Entry	R	R′	% Yield[a]
1	H	H	87
2	H	p-Me	90
3	H	p-OMe	89
4	2,4,6-Me	p-Me	0[b]
5	p-Cl	H	78
6	p-Cl	p-Me	94
7	p-Cl	m-Me	95
8	p-Cl	o-Me	92
9	p-Cl	2-Naphthyl	93
10	p-Cl	p-OMe	95
11	p-Cl	m-OMe	96
12	p-Cl	p-Cl	87
13	p-Cl	m-Cl	82

process, but rather the resultant conditions (no added base) were unfavourable for continued transmetallation of the boronic acid.

The scope of the catalytic additions employing ligand **6** was extended to include trifluoromethylketones (Table 5). The corresponding products were obtained in very good yields with a range of boronic acids. The reaction was tolerant of different substitution patterns on the donor (Table 5, entries 6–8) and even deactivating halogen substituents afforded excellent isolated yields of product (Table 5, entries 12 and 13). Unsurprisingly, the sterically demanding mesitylketone substrate proved unreactive (Table 5, entry 4).

Finally, investigating the scope of the arylation of simple ketones showed electronic effects consistent with those seen for aldehyde substrates (Table 6). Electron-withdrawing groups on the carbonyl compound are beneficial for reactivity, as are complementary electron-donating groups on the boronic acid.

It also appears that the nature of the ketone is of greater importance in determining the reactivity, with only the p-nitroacetophenone substrate offering reasonable conversion into product (Table 6, entries 4–6). The addition of further equivalents of boronic acid was found to provide a 68% yield of isolated product (Table 6, entry 7).

In conclusion, it is often noted that classical sulfonated phosphine ligands are less effective than their non-sulfonated ana-

logues due to the changes in electronic character of the phosphorus centre.[6b,18] We have shown that sulfonated S-Phos ligand **6**, with a phosphine remote sulfonate group, to be highly effective in rhodium-catalysed 1,2-additions of arylboronic acids in aqueous media. The superiority of **6** over **7** is attributed to the electron-donating dicyclohexylphosphine group enhancing the nucleophilicity of the aryl donor on rhodium. The results from the solvent study suggest an 'on-water' reaction may be occurring, where the reactants are dispersed as small droplets leading to a large increase in the surface area between the reactants and the aqueous phase. The effective high concentrations of reactants, coupled with the continued availability of ions from bulk solution contribute to an enhanced rate of transmetallation and ensuing insertion.[19] The aqueous solubility of the sulfonated S-Phos ligand enabled the rhodium complex to be recycled in five successive aldehyde arylations affording quantitative conversions and a 97% isolated yield of product in the final run.

Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.082.

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Table 6
Aryl-methyl ketone reactivity patterns

All reactions performed on 1.0 mmol of ketone in water (1.5 ml).
  a As determined by ¹H NMR spectroscopy, isolated yields in parentheses.
  b Using 5.0 equiv of boronic acid.

Entry	R	R′	% Conv.[a]
1	p-OMe	p-OMe	6
2	p-Me	p-OMe	13
3	p-F	p-OMe	19
4	p-NO₂	p-F	41
5	p-NO₂	p-Me	49
6	p-NO₂	p-OMe	60
7	p-NO₂	p-OMe	70 (68)[b]

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