

Dirhodium(II)-Catalyzed Cross-Coupling Reactions of Aryl Aldehydes with Arylboronic Acids in Water

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In this report, dirhodium(II) catalysts with axial phosphanes ligands were employed to catalyze cross-coupling reactions of aromatic aldehydes with arylboronic acids to generate ketones in neat water. The overall reaction is proposed to occur through a cascade process involving the dirhodiumcatalyzed addition of boronic acids to aldehydes followed by the dehydrogenative oxidation of alcohols.

Introduction

Rhodium-catalyzed addition reactions of arylboronic acids with carbonyl-containing compounds have been well documented.^[1] The rhodium metal oxidation states Rh^I,^[2] Rh^{II},^[3] and Rh^{III[4]} are all able to catalyze 1,2-addition reactions of arylboronic acids to aldehydes by forming diarylcarbinols as final products. Owing to the potential cooperativity between the two metal sites, binuclear dirhodium(II) complexes are attractive systems of study for the activation of organic substrates.^[3e] Recently, Gois and coworkers reported that dirhodium(II) complexes with unique paddlewheel structures^[3d] bind axially to N-heterocyclic carbene (NHC) ligands and catalyze the arylation reaction in high yields.^[3a-3c] Direct cross-coupling of aryl-boronic acids and aldehydes to generate diaryl ketones has

attracted considerable attention and has emerged as a powerful method in organic synthesis.^[5] However, reports on the use of rhodium catalysts to generate diaryl ketones are so far very limited.^[6] To the best of our knowledge, the pioneering example was the synthesis of diaryl ketones from potassium trifluoro(organo)borates or arylboronic acids with aryl aldehydes catalyzed by rhodium(I) by Genet and co-workers.^[6a,6c,6d] In our laboratory, we are interested in developing highly efficient catalysts by combining dirhodium compounds with various axial ligands^[3,7] and exploring the possibility of using these complexes to catalyze chemical transformations. Herein, we describe the application of dirhodium(II)/phosphane complexes in water to catalyze a cascade reaction of arylboronic acids with aldehydes to synthesize diaryl ketones (Scheme 1).



Scheme 1. DME = dimethoxyethane.

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Results and Discussion

Gois and co-workers reported that NHC ligands bind axially to $Rh_2(OAc)_4$ to catalyze addition reactions of organoboronic acids with aldehydes to yield diarylmeth-

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anols.^[3a–3c] Both alkyl/arylphosphanes and NHC ligands are generally considered poor π acceptors and strong δ donors. However, the conical shape of phosphane ligands can be significantly different from the planar shape of NHC ligands. To understand how the phosphane ligands would affect the overall reactivity of dirhodium(II) catalysts, the addition reaction of 4-methoxyaldehyde (1a) and phenylboronic acid (2a) catalyzed by dirhodium(II) acetate with phosphane ligands was chosen as the initial model for investigation.

We first chose PPh₃ as the ligand and the diarylmethanol was successfully formed in DME/water with KOtBu at 90 °C under an atmosphere of N₂ after 24 h. Changing the base to K₂CO₃ prevented the reaction. Interestingly, if the reaction was conducted in neat water with K₂CO₃ as

Table 1. Optimization of the reaction conditions.^[a]

the base, although the reaction was heterogeneous, we obtained 4-methoxybenzophenone (**3a**) in 16% yield (Table 1, entry 3). Encouraged by these results, various phosphane ligands including selected Buchwald ligands (e.g., RuPhos, BreetPhos) were tested. Results showed that $P(nBu)_3$ was the best ligand, which led to **3a** in 84% yield after purification (Table 1, entries 4–7). The reaction was less efficient if the NHC IMes·HCl ligand was employed (Table 1, entry 8). Almost no ketone product was produced if organic solvents were added to the reaction system (Table 1, entries 9 and 10). This indicated that neat water was essential for the generation of ketone **3a** if K_2CO_3 was used as the base. Further studies revealed that the dirhodium catalyst, the base, and the ligands were all needed for this reaction (Table 1, entries 12–14). The



Entry	Ligand	Solvent	Base	Yield [%] ^[b]
1 ^[c]	PPh ₃	DME/H ₂ O	tBuOK	_
2 ^[d]	PPh ₃	DME/H ₂ O	K_2CO_3	_
3	PPh ₃	H ₂ O -	K ₂ CO ₃	16
4	$P(nBu)_3$	H ₂ O	K_2CO_3	84
5	$P(OPh)_3$	H ₂ O	K_2CO_3	20
6	RuPhos	H ₂ O	K_2CO_3	53
7	BrettPhos	H ₂ O	K_2CO_3	19
8	IMes·HC1	H ₂ O	K_2CO_3	22
9 ^[d]	$P(nBu)_3$	DME/H ₂ O	K_2CO_3	trace
10 ^[e]	$P(nBu)_3$	toluene/H ₂ O	K_2CO_3	trace
11 ^[f]	$P(nBu)_3$	H_2O	K_2CO_3	61
12	_	H ₂ O	K_2CO_3	trace
13 ^[g]	$P(nBu)_3$	H_2O	K_2CO_3	_
14	$P(nBu)_3$	H ₂ O	_	<5
15	$P(nBu)_3$	H_2O	NaHCO ₃	53
16	$P(nBu)_3$	H ₂ O	$K_3PO_4 \cdot 7H_2O$	66
17	$P(nBu)_3$	H ₂ O	KOH	86
18	$P(nBu)_3$	H ₂ O	K_2CO_3 (3 equiv.)	38
19	$P(nBu)_3$	H ₂ O	tBuOK	77
20 ^[h]	$P(nBu)_3$	H ₂ O	K_2CO_3	31

[a] Unless otherwise noted, all reactions were performed by using aldehyde **1a** (1.00 mmol), arylboronic acid **2a** (2.00 mmol), $Rh_2(OAc)_4$ (3 mmol-%), ligand (6 mol-%), and base (1.00 mmol) in solvent (1 mL) at 90 °C for 24 h under an atmosphere of N₂. Cy = cyclohexyl. [b] Yield of isolated product. [c] DME/water = 5:1. The reaction gave the diarylmethanol in 88% yield. [d] DME/water = 5:1. [e] Toluene/water = 5:1. [f] Ligand (3 mol-%). [g] No rhodium catalyst was used. [h] $Rh_2(OAc)_4$ (1 mol-%) and ligand (2 mol-%).

amount of axial ligand was essential to the yield of the reaction. If a lower amount of $P(nBu)_3$ was used, the addition reaction gave a lower yield (Table 1, entry 11). A series of bases was also examined: KOH and K₂CO₃ gave nearly identical results, and an excess amount of the base (3 equiv.) did not improve the yield of ketone **3a** (Table 1, entries 15–19). Upon lowering the amount of $Rh_2(OAc)_4$ to 1 mol-% and the amount of $P(nBu)_3$ to 2 mol-%, the addition reaction was sluggish and afforded ketone **3a** in 31% yield (Table 1, entry 20).

Under similar reaction conditions, benzaldehydes with various electron-withdrawing and electron-donating substituents (i.e., 1b-j) all reacted with 2a and 2b smoothly to afford the corresponding diaryl ketones (i.e., 3b-j, v-x) in good yields (Table 2, entries 1–9, 21–24). Sterically bulkier aldehydes such as 1-naphthylbenzaldehyde (1k) and 2-methoxybenzaldehyde (1l) also reacted with 2a to afford diaryl ketones 3k and 3l, albeit in lower yields (Table 2, entries 10 and 11). Similarly, the heterocyclic aldehyde 1-formylfuran (1m) and the aliphatic aldehyde cyclohexane-carbaldehyde (1n) were less effective substrates; they reacted with 2a by generating the corresponding aryl ketones in 55 and 30% yield, respectively (Table 2, entries 12 and 13). Incubating 4-hydroxybenzaldehyde (1o)

Table 2. Dirhodium-catalyzed formation of diaryl ketones from aldehydes and arylboronic acids. $^{[a]}$

	$B(OH)_2$	Rh ₂ (OAc) ₄ , P(<i>n</i> Bu) K ₂ CO ₃ H ₂ O, 90 °C, 24 h		
	1a–o 2a–g		3b–x	R-
Entry	R ¹	R ²	Product	Yield [%] ^[b]
1	C_6H_5 (1b)	Н (2а)	3b	70
2	$4-MeC_{6}H_{4}$ (1c)	H (2a)	3c	54
3	$3-OMeC_{6}H_{4}$ (1d)	H (2a)	3d	54
4	2-naphthyl (1e)	H (2a)	3e	76
5	$(3,4-OCH_2O)C_6H_3$ (1f)	H (2a)	3f	62
6	$3,4,5-(OMe)_3C_6H_2$ (1g)	H (2a)	3g	72
7	$4-CF_{3}C_{6}H_{4}$ (1h)	H (2a)	3h	80
8	$4-ClC_{6}H_{4}$ (1i)	H (2a)	3i	87
9	$4-FC_{6}H_{4}(1j)$	H (2a)	3j	64
10	1-naphthyl (1k)	H (2a)	3k	37
11	$2-OMeC_{6}H_{4}$ (11)	H (2a)	31	39
12	1-furyl (1m)	H (2a)	3m	55
13	Cy (1n)	H (2a)	3n	30
14	$4-OHC_{6}H_{4}$ (10)	H (2a)	30	_
15	$4-OMeC_{6}H_{4}$ (1a)	4-OMe (2b)	3р	81
16	$4-OMeC_{6}H_{4}$ (1a)	2-OMe (2c)	3q	37
17	$4-OMeC_{6}H_{4}$ (1a)	2-naphthyl (2d)	3r	38
18	$4-OMeC_{6}H_{4}$ (1a)	4-Cl(2e)	3s	55
19	$4-OMeC_{6}H_{4}$ (1a)	4-CF ₃ (2f)	3t	40
20	$4-OMeC_{6}H_{4}$ (1a)	4-CN (2g)	3u	_
21	1-naphthyl (1k)	4-OMe (2b)	3v	62
22	$4-ClC_{6}H_{4}$ (1i)	4-OMe (2b)	3s	51
23	$3,4,5-(OMe)_3C_6H_2$ (1g)	4-OMe (2b)	3w	68
24	$4-FC_{6}H_{4}$ (1j)	4-OMe (2b)	3x	45

[a] Unless otherwise noted, all reactions were performed by using aldehyde **1** (1.00 mmol), arylboronic acid **2** (2.00 mmol), $Rh_2(OAc)_4$ (3 mol-%), $P(nBu)_3$ (6 mol-%), and K_2CO_3 (1.00 mmol) in H_2O (1 mL) at 90 °C for 24 h under an atmosphere of N_2 . [b] Yield of isolated product.



with **2a** did not afford any coupling product, which indicated that this reaction was not compatible with hydroxy substituents on the aromatic ring of benzaldehyde **1**. We also tested several arylboronic acids to react with 4-methoxybenzaldehyde (**1a**; Table 2, entries 15–20). Electronrich 4-methoxyphenylboronic acid (**2b**) generated the coupled product in good yields, whereas 4-Cl- and 4-CF₃-substituted boronic acids **2e** and **2f** gave moderate yields of the ketone, and 4-CN-substituted boronic acid **2g** did not yield any of the desired coupling product. Similarly, bulkier arylboronic acids such as 2-methoxyphenylboronic acid (**2c**) and 2-naphthylboronic acid (**2d**) were less reactive, and they delivered low yields of the ketone products.

In investigating the reaction mechanism of these dirhodium-catalyzed coupling reactions, we found that diphenylmethanols formed quickly at the early stage of the reaction and were then oxidized to diaryl ketones slowly afterwards. This phenomena was described previously in Genet's reaction catalyzed by Rh^{I.[6a,6d]} Addition reactions of arylboronic acids with aldehydes to form diarylmethanol catalyzed by rhodium(I) or dirhodium(II) have been well documented.^[2,3a-3c,4] Thus, we focused on the mechanism of diaryl ketone formation. Different from Genet's reaction, in which the cosolvent acetone as a hydride acceptor was crucial to generate the desired ketone products,^[6a,6d] only water was used as the solvent in our reaction, and this prompted us to explore possible alternative pathways and the involvement of water in these reactions. After treating diphenylmethanol 4a under the reaction conditions without adding an arylboronic acid, ketone 3a was formed in 91% yield (Table 3, entry 4). In the absence of a metal catalyst or ligand, oxidation to the ketone did not proceed (Table 3, entries 1 and 2). The above results indicated that diarylmethanol 4a was anaerobically oxidized to diaryl ketone 3a under the reaction conditions. Notably, water is crucial to the oxidation (Table 3, entries 3) and 4) and hydrogen is produced in this oxidation process (see the Supporting Information).

Table 3. Anaerobic oxidation of diarylmethanol to diaryl ketone product. $^{\left[a\right] }$

0	OH 4a	Rh cataly K ₂ C solv 90 °C, 2	st, ligand CO ₃ vent 24 h, N ₂	O Ja
Entry	Catalyst	Ligand	Solvent	Yield [%] ^[b]
1	_	$P(nBu)_3$	H ₂ O	trace
2	Rh ₂ (OAc) ₄	_	H_2O	trace
3	$Rh_2(OAc)_4$	$P(nBu)_3$	DME	<5
4	Rh ₂ (OAc) ₄	$P(nBu)_3$	H_2O	91

[a] Unless otherwise noted, all reactions were performed by using alcohol **4a** (1.00 mmol), $Rh_2(OAc)_4$ (3 mol-%), PR_3 (6 mol-%), and K_2CO_3 (1.00 mmol) at 90 °C for 24 h under an atmosphere of N_2 . [b] Yield of isolated product.

On the basis of the above results and literature reports,^[1,6] we propose that the reaction occurs through a cascade process involving dirhodium-catalyzed addition of

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the boronic acid to the aldehyde^[3a-3c] followed by dehydrogenative oxidation of an alcohol.^[8] For the formation of the diarylmethanol coupling product, according to the mechanism proposed by Gois and co-workers,^[3b] the dirhodium catalyst activates the boronic acid with the aid of the phosphane ligand and the base; then, direct transfer of the phenyl group from the boron to the aldehyde occurs. Subsequently, the formed diarylmethanol reacts with the dirhodium catalyst to give a rhodium alkoxide. After βhydride elimination of the rhodium alkoxide, the aryl ketone is produced as the dehydrogenated product. Regarding the dehydrogenation and hydrogen-release mechanism, Saito and co-workers previously reported the selective dehydrogenation of 2-propanol catalyzed by Rh₂(OAc)₄ by adding PPh₃ in situ.^[9] The unique dirhodium complex structure^[3d] and the tuning effect of the axial ligands^[7,10] may account for this transformation. Detailed mechanistic studies, especially the water effect, are currently underway in our laboratory.

Conclusions

In summary, we developed an effective method for the synthesis of aryl ketones from arylboronic acids with aldehydes in water through a cascade catalytic procedure and demonstrated that dirhodium complexes with axial phosphane ligands are an efficient catalyst combination. We also found that these coupling reactions are highly dependent on the solvent, and neat water proved to be essential in these reactions if K_2CO_3 was used as the base. Future work is aimed at elucidating a detailed mechanism and the application of this catalyst system.

Experimental Section

General Procedures for Products: $Rh_2(OAc)_4$ (0.009 mmol, 3 mol-%), aldehyde (0.3 mmol, 1.0 equiv.), arylboronic (0.6 mmol, 2.0 equiv.), and K_2CO_3 (0.6 mmol, 1.0 equiv.) were added to a tube. The septum-sealed tube was evacuated and refilled with nitrogen three times. Water (1.0 mL) was added by syringe. Then, tri-*n*-butylphosphane (0.018 mmol, 6 mol-%) was added with stirring. The reaction mixture was heated in an oil bath at 90 °C for 24 h. After cooling down the reaction mixture to ambient temperature, it was extracted with ethyl acetate (3 × 5 mL) and washed with water (2 × 10 mL). The ethyl acetate layer was separated and dried with Na₂SO₄. After evaporation of the solvent, the residue was purified by flash column chromatography (ethyl acetate/hexane) to give the desired diaryl ketone.

Supporting Information (see footnote on the first page of this article): Experimental procedures, spectroscopic data, and copies of the ¹H NMR and ¹³C NMR spectra.

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