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Synthesis of arylketones by ruthenium-catalyzed cross-coupling of aldehydes with arylboronic acids†

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The first ruthenium-catalyzed cross-coupling of aldehydes with arylboronic acids is reported. Various aliphatic and aromatic aldehydes are transformed to the corresponding arylketones. A total of 31 examples with moderate to excellent yields are presented, together with the results of an initial mechanistic investigation.

Arylketones occur widely in a myriad of compounds of pharmaceutical, agrochemical, biological, and materials of interest. They also represent versatile intermediates for further transformations in synthetic chemistry.[1] Conventional routes to the synthesis of arylketones have relied heavily upon Friedel–Crafts acylations of arenes.[2] Common drawbacks of these processes are tedious procedures involved, and more importantly, low regioselectivity and functional group tolerance. In view of these shortcomings, alternative synthetic strategies for arylketones have been actively pursued. Recent research efforts have resulted in significant achievements in this field. Hydroacylation of olefins represents one of the most promising methods for producing ketones,[3] although it generally requires chelation assistance to suppress undesired decarbonylation reaction. Heck-type reaction of aryl halides with aldehydes offers another efficient approach. However, initial results have been limited to aryl iodide and have afforded alkyl aryl ketones in low yields.[4] Recently, Xiao and co-workers reported the elegant palladium-catalyzed coupling of aldehydes with aryl bromides or chlorides, resulting in alkyl aryl ketones in good yields.[5] In addition, Hartwig *et al.* developed acylation of aryl halides with *N*-pyrazyl aldimines or *N*-*tert*-butylhydrazones, followed by hydrolysis.[6]

Recently, Genet[7] and others,[8] in their pioneering work, developed rhodium-catalyzed coupling of aryl boron reagents with aldehydes. Using chelation assistance strategy, Jun *et al.* described ruthenium-catalyzed coupling of aldimines with arylboronates to form aromatic ketimines, which generate ketones upon hydrolysis.[9] One example of a ruthenium-catalyzed arylation of aldehydes with arylboronic acids to form alcohol was recently published by Yamamoto and Miyaura *et al.*[10] However, to the best of our knowledge, direct cross-coupling of arylboronic acids with aldehydes to form ketones, catalyzed by ruthenium complexes, has not been reported to date.[11] We expect this alternative strategy may open up a new pathway for preparation of ketones. Furthermore, not unimportantly, ruthenium is much cheaper than rhodium.

As part of our investigations into Ru chemistry,[12] we initially examined coupling of benzaldehyde (**1a**) with 4-methoxyphenylboronic acid (**2a**) to furnish aryl ketone, using ruthenium complexes. After exploring a wide array of conditions, we determined that 2.5 mol% $[Ru(CO)_3Cl_2]_2$/10 mol% *t*-$Bu_3P{\cdot}HBF_4$/2.0 equiv. pinacolone/2.0 equiv. $K_3PO_4{\cdot}3H_2O$ in toluene/H_2O at 100 °C furnishes an excellent yield (91%) of the desired cross-coupling product **3a** (Table 1, entry 1). Table 1 provides information on the impact of various reaction parameters on the efficiency of this new cross-coupling process. As expected, in the absence of a ruthenium catalyst, no cross-coupling occurs (Table 1, entry 2). Replacement of $[Ru(CO)_3Cl_2]_2$ with $[Ru(cymene)Cl_2]_2$ or $RuCl_3$ leads to a drop in yield (Table 1, entries 3 and 4). Without phosphine addition, the conversion is low, giving only trace amounts of product **3a** (Table 1, entry 5). Notably, the use of PCy_3, $PCy_3{\cdot}HBF_4$ or PPh_3 lowered the yield (Table 1, entries 6–8), and dppe retarded the reaction (Table 1, entry 9). In addition, the presence of base is essential for this transformation (Table 1, entry 10). Finally, replacement of pinacolone with acetone resulted in decreased yield (Table 1, entry 11).

The scope of the coupling of aldehydes with 4-methoxyphenylboronic acid (**2a**) is summarized in Table 2. Both aliphatic and aromatic aldehydes can be successfully converted to the corresponding ketones. The reaction tolerates a wide range of substituents on aromatic nuclei, for example halide, CF_3, nitrile, nitro, amine, BocO, OTs, and ether. Notably, *ortho* substituted aromatic aldehydes also participated in the transformation and the desired products were obtained in satisfactory yields (Table 2, products **3g** and **3h**). In the case of heteroarene aldehydes, that is, 2-furaldehyde and 2-thiophenaldehyde, the coupling products were obtained in 96% and 45% yields, respectively (Table 2, products **3o** and **3s**).

The scope of boronic acids was then investigated using 4-chlorobenzaldehyde as a coupling partner. These results

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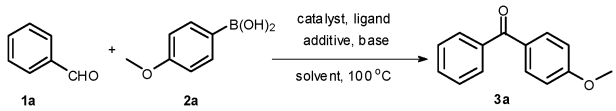
Table 1 Optimization of reaction conditions[a]

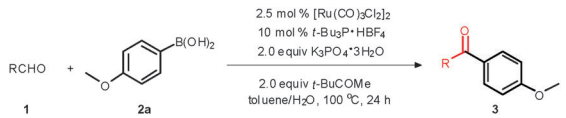


1a 2a 3a

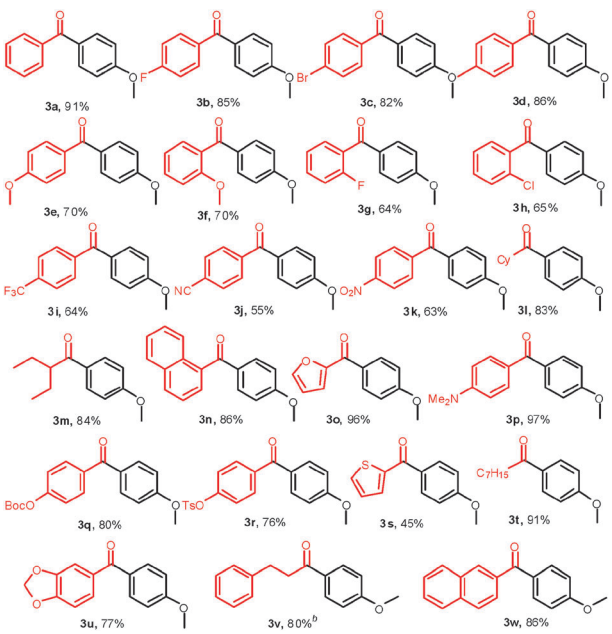
Entry	Catalyst	Ligand	Additive	Base	Yield[b]
1	$[Ru(CO)_3Cl_2]_2$	t-$Bu_3P{\cdot}HBF_4$	t-BuCOMe	$K_3PO_4{\cdot}3H_2O$	91%
2	—	t-$Bu_3P{\cdot}HBF_4$	t-BuCOMe	$K_3PO_4{\cdot}3H_2O$	N.O.[c]
3	$[Ru(cymene)Cl_2]_2$	t-$Bu_3P{\cdot}HBF_4$	t-BuCOMe	$K_3PO_4{\cdot}3H_2O$	83%
4	$RuCl_3$	t-$Bu_3P{\cdot}HBF_4$	t-BuCOMe	$K_3PO_4{\cdot}3H_2O$	Trace
5	$[Ru(CO)_3Cl_2]_2$	—	t-BuCOMe	$K_3PO_4{\cdot}3H_2O$	Trace
6	$[Ru(CO)_3Cl_2]_2$	PCy_3	t-BuCOMe	$K_3PO_4{\cdot}3H_2O$	44%
7	$[Ru(CO)_3Cl_2]_2$	$PCy_3{\cdot}HBF_4$	t-BuCOMe	$K_3PO_4{\cdot}3H_2O$	37%
8	$[Ru(CO)_3Cl_2]_2$	PPh_3	t-BuCOMe	$K_3PO_4{\cdot}3H_2O$	13%
9	$[Ru(CO)_3Cl_2]_2$	dppe	t-BuCOMe	$K_3PO_4{\cdot}3H_2O$	Trace
10	$[Ru(CO)_3Cl_2]_2$	t-$Bu_3P{\cdot}HBF_4$	t-BuCOMe	—	N.O.[c]
11	$[Ru(CO)_3Cl_2]_2$	t-$Bu_3P{\cdot}HBF_4$	MeCOMe	$K_3PO_4{\cdot}3H_2O$	82%[d]

[a] Reaction conditions: benzaldehyde (0.5 mmol), 4-methoxyphenylboronic acid (1.25 mmol), catalyst (0.0125 mmol), ligand (0.05 mmol), pinacolone (1.0 mmol), $K_3PO_4{\cdot}3H_2O$ (1.0 mmol) in 2.0 mL toluene and 0.2 mL water at 100 °C for 24 h unless noted otherwise. [b] Isolated yield. [c] Not observed. [d] In a sealed tube.

Table 2 Cross-coupling of aldehydes with 4-methoxyphenylboronic acid[a]

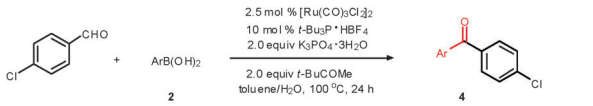


1 2a 3

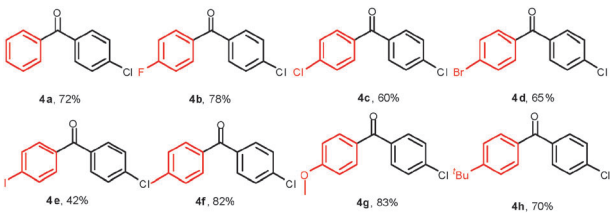


[a] Reaction conditions: aldehyde (0.5 mmol), 4-methoxyphenylboronic acid (1.25 mmol), catalyst (0.0125 mmol), ligand (0.05 mmol), pinacolone (1.0 mmol), $K_3PO_4{\cdot}3H_2O$ (1.0 mmol) in 2.0 mL toluene and 0.2 mL water at 100 °C for 24 h unless noted otherwise. [b] 48 h.

Table 3 Cross-coupling of 4-chlorobenzaldehyde with boronic acids[a]



2 4



[a] Reaction conditions: aldehyde (0.5 mmol), 4-methoxyphenylboronic acid (1.25 mmol), catalyst (0.0125 mmol), ligand (0.05 mmol), pinacolone (1.0 mmol), $K_3PO_4{\cdot}3H_2O$ (1.0 mmol) in 2.0 mL toluene and 0.2 mL water at 100 °C for 24 h unless noted otherwise.

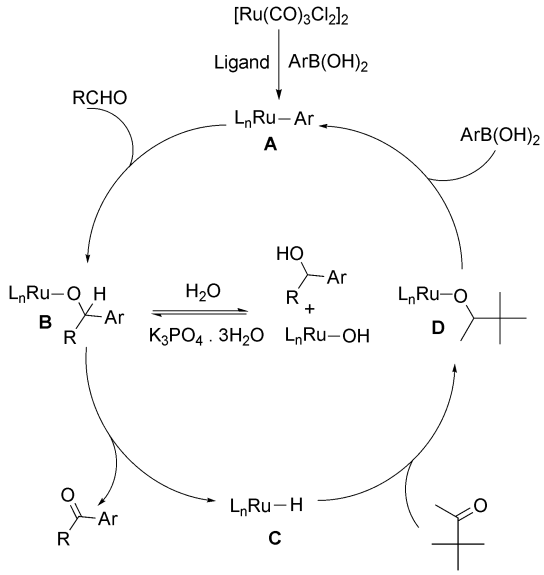
indicate that boronic acids with electron-withdrawing or electron-donating groups proceeded well and the desired coupling products were obtained in moderate to high yields (Table 3).

Complete conversion of benzaldehyde **1a** was observed under the optimized conditions for 0.5 h. Ketone **3a** and secondary alcohol **5** were achieved with an excellent combined yield, which implies that secondary alcohols may serve as reaction intermediates in the transformation (eqn (1), see supporting information†). Subjecting secondary alcohol **5** to the reaction, the desired ketone **3a** was generated in high yield (eqn (2), see supporting information†).

The kinetic isotope effect (KIE) was investigated under the standard reaction conditions. This small isotopic effect (KIE = 1.06) was observed in the transformation (eqn (3), see supporting information†). In addition, no decarbonylation was observed in the transformation,[13] which implies that aldehyde C–H activation is not involved in the catalytic cycle.

Further experiments were carried out to elucidate the mechanism. In competition experiments carried out using **5** and *D*-**5**, measurement of deuterium (KIE = 3.13) suggests that hydrogen abstraction from alcohol is probably rate-limiting during the transformation (eqn (4), see supporting information†).

Based upon the above results and literatures,[7] a plausible mechanism was proposed, as outlined in Scheme 1.



Scheme 1 Plausible catalytic cycle.

This mechanism includes (1) transmetalation of boronic acid to $[Ru(CO)_3Cl_2]_2$ to form an arylruthenium complex **A**,[14] (2) insertion of aldehyde into the ruthenium-carbon bond to give an alkoxo-ruthenium intermediate **B**, (3) β-hydride elimination from **B**, a rate-determining step, to release the diaryl ketone and hydridoruthenium complex **C**, (4) insertion of pinacolone into the ruthenium-hydrogen bond to give an alkoxo-ruthenium intermediate **D**, (5) transmetalation of boronic acid to intermediate **D**, allowing the regeneration of arylruthenium complex **A**.

Further experiments were performed to verify the presumed catalytic pathways. Recently, Darses and Genet reported Rh-catalyzed cross-coupling of aldehydes with boron reagents to access ketones. In the absence of base, secondary alcohol, instead of ketone, was observed in the transformation.[7b] The role of base was the regeneration of an alkoxo-rhodium intermediate. In sharp contrast, both secondary alcohol and ketone were achieved even in the absence of base in our transformation (eqn (6), see supporting information†). This suggests that base is not essential for generation of arylruthenium intermediate **A** or regeneration of alkoxo-ruthenium intermediate **B**.

Reduction product, 2-naphthalenemethanol, was achieved in 29% yield in the absence of pinacolone, which implies that the insertion of 2-naphthaldehyde into the ruthenium-hydrogen bond of hydridoruthenium complex **C** is involved in the transformation (eqn (7), see supporting information†).

In summary, we have described a new protocol for synthesis of arylketones by ruthenium-catalyzed cross-coupling of aldehydes with arylboronic acids. The reaction is effective for aliphatic and aromatic aldehydes. More detailed investigations into mechanisms and further applications of this methodology are now in progress in our laboratory.

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