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New synthesis of 1,4-diketones *via* rhodium-catalysed 1,4 carbonylative addition of arylboronic acids to α,β-unsaturated ketones

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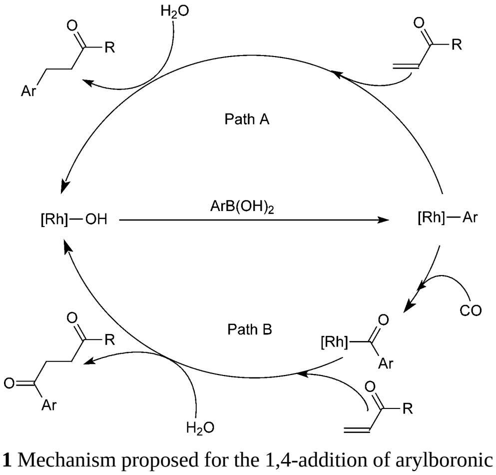
The reaction of various arylboronic acids with α,β-unsaturated ketones under CO pressure and in the presence of rhodium catalyst yields 1,4-diketones.

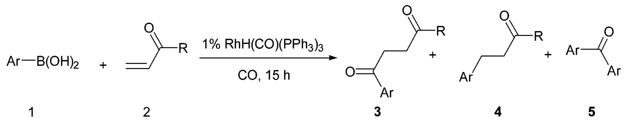
1,4-diketones are very useful intermediates for thienyl, pyrrol or furyl heterocycles synthesis.[1] A synthetic pathway for this family of derivatives is the acylation reaction of α,β-unsaturated ketones.[2] For this purpose, early acylmetal reagents were only partially successful. They often suffer from the use of toxic metal carbonyl complexes and/or stoichiometric amounts of metal. Moreover, even used in combination with a palladium catalyst these acyl sources have to be synthesised separately[3] and thus a straightforward procedure would correspond to an *in situ* generation of the acyl reagent with a catalytic amount of metal.

The 1,4-addition of arylboronic acids to α,β-unsaturated ketones catalysed by a rhodium salt proved to be relevant for C–C bond formation.[4] Later, the scope of the reaction was broadened to several other metal catalysed arylation transformations.[4a,5] As the catalytic cycle proposed an intermediate possessing a Rh–Aryl species (Scheme 1, path A),[6] we anticipated that under a CO atmosphere, a carbonylation reaction would occur to produce a metal–acyl species and ultimately lead to 1,4-diketones formation (Scheme 1, path B).

Catalytic tests confirmed this hypothesis (Scheme 2 and Table 1).† When the reaction between phenylboronic acid **1a** and methylvinylketone **2a** was performed under 1 bar CO pressure with $RhH(CO)(PPh_3)_3$ the expected carbonylated 1,4-diketone **3a** was obtained as the major product together with **4a** and **5a** (entry 1). The presence of both **3a** and **4a** indicates a competition between the known 1,4-addition reaction and the carbonylative one. The formation of **5a** was not expected and can be described as the product of carbonylative cross coupling reaction between two equivalents of phenylboronic acids. A similar reaction was observed in the unique example of a palladium catalyst.[7] It is likely that this reaction proceeds in a similar way in the present case of a rhodium catalyst.



Scheme 1 Mechanism proposed for the 1,4-addition of arylboronic acids to α,β-unsaturated ketones[6] (path A) and envisioned for its carbonylative counterpart (path B).



Scheme 2 Rhodium catalysed aroylation of enones with arylboronic acids and carbon monoxide.

Catalyst and reaction conditions were optimised in order to achieve better selectivities. At first, the influence of the ligand was checked. The phosphane free reaction was poorly efficient and products were obtained only in very low yields. Since the selectivity of the reaction was surprisingly only slightly sensitive to the phosphine nature, $RhH(CO)(PPh_3)_3$ was chosen as catalyst for the complete study of this new reaction. From a series of studies, we found that the selectivity of the reaction depends greatly on the reaction conditions.

As expected, the reaction with higher CO pressure proceeded with a preference for **3a** *versus* **4a** (entries 1 and 3). Mild reaction temperatures are necessary to limit the formation of **5a**. Increasing the reaction temperature from 80 °C to 100 °C resulted in an increase of the yield of this compound from 7% to 33% (entries 3 and 4) and this important starting boronic acid wasting probably explains the low yields in **3a** and **4a**. Lowering the reaction temperature to 60 °C allowed a better selectivity in **3a** *versus* **5a** (entry 2). The reaction is highly sensitive to the solvent nature (entries 3 and 5–7). No reaction was observed with 1,4-dioxane and the best yields were obtained with MeOH even if it was previously dried over magnesium. Thus, in marked contrast to the 1,4 addition of boronic acids to α,β-unsaturated ketones, the presence of water is not necessarily advantageous for the reaction. Although better selectivities were achieved, the yields in **3a** always remained below 50%. As it was similarly observed in the case of the rhodium catalysed Heck-type reaction of arylboronic acids with α,β-unsaturated esters, GC and GC-MS studies indicated a complete disappearance of methyl vinyl ketone together with methyl ethyl ketone formation.[8] This observation prompted us to increase the amount of methyl vinyl ketone used at the beginning of the reaction. With two equivalents of methyl vinyl ketone the yield into **3a** increased from 44% to 78% (entries 3 and 8) but higher amounts of α,β-unsaturated ketones did not afford better yields. It is noteworthy that crude MeOH, used as received works equally well

Table 1 Rhodium catalysed aroylation reaction of methylvinylketone **2a** with phenylboronic acid **1a** under CO pressure[a]

Entry	Solvent	**2a/1a** mol/mol	*P*(CO) (atm.)	*T* (°C)	**3a** (%)[b]	**4a** (%)[b]	**5a** (%)[b]
1	MeOH	1	1	80	30	18	7
2	MeOH	1	20	60	26	< 2	2
3	MeOH	1	20	80	44	4	7
4	MeOH	1	20	100	30	2	33
5	THF	1	20	80	13	< 2	7
6	THF/H_2O	1	20	80	21	3	9
7	1,4-dioxane	1	20	80	0	0	0
8	MeOH	2	20	80	78	9	7
9[c]	MeOH	2	20	80	76	7	8

[a] The reaction was carried out using phenylboronic acid (1.5 mmol), 1% $RhH(CO)(PPh_3)_3$ and 10 mL solvent for 15 h. [b] Yields determined by GC based on phenylboronic acid. [c] 1% $RhCl_3$/3 PPh_3 as catalyst.

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and no strictly deoxygenated conditions are necessary. Moreover, a simple combination of $RhCl_3$/3 PPh_3 showed the same efficiency (entry 9) and that contributes to make of this reaction an easy procedure for 1,4-diketone **3a** synthesis from readily available starting materials.

At this point of the study, it was important to check the generality of the reaction. Various substituted arylboronic acids have been successfully reacted using optimised conditions MeOH, 80 °C, 20 bars CO and 1% $RhHCO(PPh_3)_3$ with a 2:1 ratio of olefin to boronic acid (Table 2; method A).

The selectivity was largely affected by the substituent on the aryl group of the organoboronic acid used. High yields in the corresponding carbonylated products **3** are obtained with *para*-electrodonating substituents (entries 2–3). Derivatives of type **4** and **5** were obtained only in low yields and easily separated from **3** by column chromatography on alumina giving an overall isolated yield of **3** higher than 75%. Arylboronic acids with electro-withdrawing groups are less easily converted into **3** and an unsatisfactory yield of 38% is obtained with 3-chlorophenyl boronic acid (entry 4). This is mainly due to the predominant noncarbonylative process yielding **4** in 42% yield. This suggests a disfavoured carbon monoxide insertion step in the Rh–Ar bond in the case of *para*-electro-withdrawing substituents. This is not surprising as similar observations were reported in cases of stoichiometric carbonylation reactions of aryl-palladium, platinum and ruthenium complexes.[9] Higher CO pressure and lower temperature conditions were necessary to achieve better selectivities (Table 2; conditions B: 40 bars CO and 60 °C allowed the formation of the carbonylated derivative **3** in 73 % yield). The same procedure was finally successfully applied using various halo-substituted arylboronic acids (entries 5–7). Sterically hindered *ortho*-substituted arylboronic acids were hardly used in this carbonylation reaction. *o*-Tolylboronic acid furnished **3** in 47% yield under conditions B with a significant amount of **4**.

Table 2 Rhodium catalysed aroylation reaction of α,β-unsaturated ketones under CO pressure with various arylboronic acids[a]

Entry	Ar	Method	R	**3** (%)[b]	**4** (%)[b]	**5** (%)[b]
1	C_6H_5	A	Me	78 (72)	9	7
2	4-MeC_6H_4	A	Me	81 (78)	6	3
3	4-$MeOC_6H_4$	A	Me	80 (76)	6	3
4	3-ClC_6H_4	A	Me	38	42	4
5	3-ClC_6H_4	B	Me	73	8	5
6	4-ClC_6H_4	B	Me	73	5	2
7	4-FC_6H_4	B	Me	71	7	2
8	2-MeC_6H_4	B	Me	47	35	< 2
9	C_6H_5	A	C_6H_5	55	nd	nd
10	C_6H_5	B	Et	76	nd	nd

[a] Reaction were carried out using arylboronic acid (1.5 mmol) and 1% $RhH(CO)(PPh_3)_3$ in 10 mL MeOH for 18 h. Method A: 20 bars CO and 80 °C; Method B: 40 bars CO and 60 °C. [b] Yields were determined by GC based on the arylboronic acid, isolated yields are given in parentheses.

Activated olefins are necessary for the reaction to proceed and simple α-olefins failed to react except ethylene which led to small yields in propiophenone. Ethyl vinyl ketone was reacted in a similar way and moderate yields were obtained with phenyl vinyl ketone, probably because of its easy polymerisation (entries 9 and 10).

In conclusion, we have developed a new and efficient catalytic process for acylation of enones yielding 1,4-diketones. The acylation reagent is catalytically generated *in situ* from a combination of arylboronic acid, carbon monoxide and rhodium–triphenylphosphine complex. Further studies aimed at the generalisation of this new process to other unsaturated substrates are under investigation.

Notes and references

† *General procedure* : A 100 mL stainless steel autoclave equipped with a magnetic stirrer was charged with phenylboronic acid (**1a**, 0,183 g, 15 mmol) and $RhH(CO)(PPh_3)_3$ (13 mg, 0,15 mmol). The autoclave was evacuated and filled with dinitrogen. A solution of methylvinylketone (**2a**, 0,244 mL, 3 mmol) and undecane (internal standard for GC analysis) in MeOH (10 mL) was prepared in a Schlenk tube under dinitrogen. This was then transferred to the stainless steel autoclave *via* a cannula and stirred under dinitrogen for 2 min. CO was charged at the required pressure and the mixture was warmed at the prerequisite temperature. At the end of the reaction, the autoclave was cooled in an ice bath, vented, and the products were analysed by gas chromatography analysis.

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