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Rhodium catalysed addition of boronic acids to anhydrides: a new method for the synthesis of ketones

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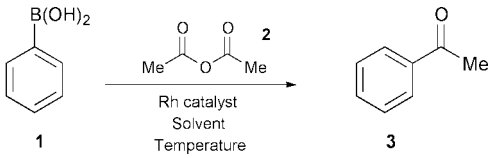
Received (in Cambridge, UK) 22nd August 2001, Accepted 26th September 2001
First published as an Advance Article on the web 24th October 2001

The efficient transmetalation from boron to rhodium is exploited in a new synthesis of aryl and alkenyl ketones.

The rhodium catalysed addition of boronic acids to organic electrophiles has recently emerged as an important tool for organic synthesis.[1] An efficient transmetalation between boron and rhodium permits the addition of organoboronic acids to a range of activated olefins.[2] Significant advances have also been made in the coupling of unactivated olefins in aqueous media.[3] Further to this the addition of aryl boronic acids to aldehydes and imines has been achieved.[4] The mechanism of these transformations is proposed to involve transmetalation between the boronic acid and the rhodium(I) complex to afford an R–Rh(I) species. The nucleophilic R group then adds to the coordinated electrophile yielding either a Rh bound enolate or alkoxide which is subsequently hydrolysed. As part of our research programme developing catalysts for the functionalisation of aromatics, we were interested in the boron–rhodium transmetalation process as a means to promote the equivalent of a Friedel–Crafts acylation reaction of deactivated aryl derivatives. This is a demanding transformation which is not readily achieved by even the most effective Lewis acid catalysts.[5] In this communication we wish to report our development of an efficient rhodium catalysed addition reaction that allows the synthesis of ketones from boronic acids under mild conditions.



Scheme 1 Rhodium catalysed acylation.

Table 1 Rhodium catalysed addition of **1** to acetic anhydride **2**

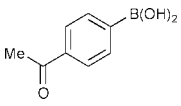
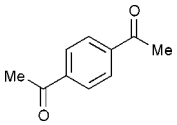
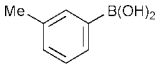
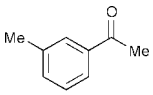
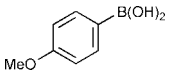
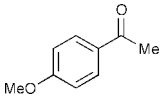
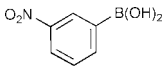
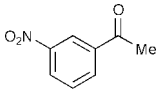
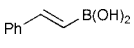
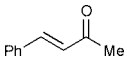
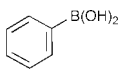
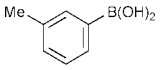
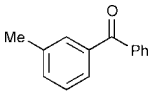
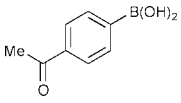
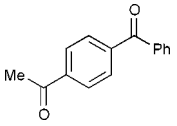
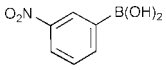
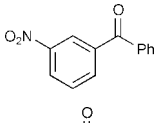
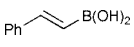
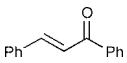
Entry	Catalyst	Solvent (Temp./°C)	Yield of 3 (%)
1	—	Dioxane (100)	0
2	[Rh(acac)(ethylene)$_2$]	Dioxane (100)	0
3	[Rh(acac)(ethylene)$_2$]	DME–H_2O (65)	0[a]
4	[Rh(acac)(cod)]	Dioxane (100)	16
5	[Rh(acac)(cod)]	DME–H_2O (65)	18[a]
6	[Rh(acac)(nbd)]	Dioxane (100)	27
7	[Rh(acac)(nbd)]	DME–H_2O (65)	29[a]
8	[Rh(nbd)Cl]$_2$	Dioxane (100)	20
9	[Rh(cod)Cl]$_2$	Dioxane (100)	57
10	[Rh(OAc)$_2$]$_2$	Dioxane (100)	27
11	$RhCl_3{\cdot}3H_2O$	Dioxane (100)	0
12	[Rh(ethylene)Cl]$_2$	Dioxane (100)	83
13	[Rh(ethylene)Cl]$_2$	DME–H_2O (65)	84[a]
14	[Rh(ethylene)Cl]$_2$	Toluene (100)	17
15	[Rh(ethylene)Cl]$_2$	THF (65)	37
16	[Rh(ethylene)Cl]$_2$	DME (65)	85[b]
17	[Rh(ethylene)Cl]$_2$	DME (20)	76[c]

[a] DME–H_2O (6:1). [b] Yield after 2 hours. [c] Yield after 16 hours.

To demonstrate this concept, initial experiments examined the reaction of phenylboronic acid (1.6 equiv.) **1** with acetic anhydride **2** in the presence of 5 mol% of various rhodium complexes (Scheme 1).[6] As summarised in Table 1, the formation of acetophenone **3** is symptomatic of an effective protocol for ketone synthesis.

The first point to note is that in the absence of catalyst no product formation is observed. It was interesting to learn that the Rh(acac) complexes favoured for addition to activated olefins, were not particularly effective in this case (entries 2–7). Similarly, the use of [Rh(OAc)$_2$]$_2$ and $RhCl_3{\cdot}3H_2O$ afforded disappointing results (entries 10 and 11). Gratifyingly, the use of [Rh(alkene)Cl]$_2$ complexes showed more promise (entry 9)

Table 2 Rhodium catalysed synthesis of ketones

Entry	Boronic acid	Product	Yield (%)
1			86
2			68
3			67
4			56
5			54
6			76
7			70
8			88
9			59
10			74

 DOI: 10.1039/b107633g

resulting in the formation of **3** in excellent overall yield in the best case (entry 12). The choice of solvent had a clear effect on the efficiency of the reaction (entries 12–16) with the reaction proceeding smoothly in dioxane and 1,2-dimethoxyethane (DME). The insensitivity of this protocol towards air and water (entry 13) is extremely beneficial from a practical perspective. At 65 °C in DME the reaction was complete within two hours, whilst at room temperature the reaction required 24 hours to afford comparable yields (entries 16 and 17). Furthermore, the catalyst loading could be lowered to 1.5 mol% with the product **3** being obtained in an 87% yield after 16 hours. Upon lowering to 0.1 mol% of catalyst, a modest 33% of **3** was isolated after the same period of time.

Under the optimised conditions the reaction was examined with respect to the scope of the boronic acid (Table 2).† An attractive feature of this methodology is the commercial availability of a wide range of boronic acids. An important point to note about the presented reaction is the regiospecific formation of product with the electrophile substituting the boronic acid group. Therefore, whilst electronic effects (inductive and resonance) may influence the rates of the reactions, as a consequence of the nucleophilicity dictating the transmetalation and transfer processes, the composition of product is unaffected by the nature and position of substituent in the starting boronic acid. This offers a significant tactical advantage over Lewis acid catalysed electrophilic substitution processes. Thus, the reaction can be designed to mirror typical electrophilic substitution reactions (Table 2, entry 3). Conversely, the formation of *meta*- or *para*-substituted deactivated aromatics can be achieved in excellent isolated yield (Table 2, entries 1, 2 and 4). The results also confirm the scope of the reaction with the alternative electrophile, benzoic anhydride (Table 2, entries 6–10). Furthermore, the reaction can be extended to alkenylboronic acids with no significant loss in efficiency. At the present time, difficulties have been encountered in extending the methodology to acid chlorides.[7] Further investigations are directed towards accomplishing this and the addition of organoboronic acids to other electrophiles.

In summary, a new rhodium catalysed addition of boronic acids has been developed that allows the synthesis of ketones. This transformation proceeds in good yield for a range of boronic acids. Importantly, this new methodology offers specific advantages over traditional Lewis acid catalysed acylation reactions in that it allows the regiospecific functionalisation of activated, unactivated and deactivated aromatics.

C. G. F. thanks Astra-Zeneca for a generous award from their strategic research fund.

Notes and references

† *General experimental procedure*: to a pressure tube charged with $[Rh(ethylene)Cl]_2$ (0.006 mmol, 1.5 mol%) was added 1,4-dioxane (4 ml), boronic acid (0.56 mmol) and anydride (1 ml of 0.4 M solution). The tube was sealed, placed in a cold oil bath which was then heated to the required temperature and stirred for 16 hours. The mixture was allowed to cool to room temperature then worked up by extracting with ethyl acetate, washing with brine, drying over magnesium sulfate and concentrating *in vacuo*. The crude product was then purified by flash chromatography (ethyl acetate–hexane, 1:8 by volume). All the products have been satisfactorily characterised by ^{1}H NMR, ^{13}C NMR and IR spectroscopy.

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