Ruthenium-catalyzed 1,4-Addition of Organoboronic Acids to α,β-Unsaturated Ketones

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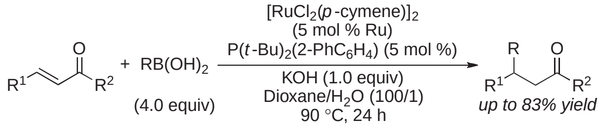
A ruthenium-catalyzed 1,4-addition of organoboronic acids to α,β-unsaturated ketones has been developed. The use of 2-(di-*tert*-butylphosphino)biphenyl as the ligand in combination with $[RuCl_2(p\text{-cymene})]_2$ complex catalyzes these reactions to selectively give 1,4-adducts in good yield by effectively suppressing Heck-type and reduced products.

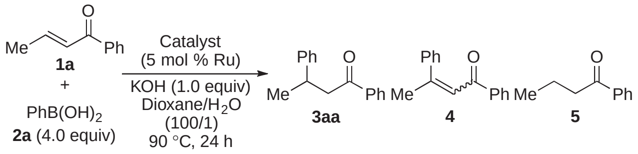
1,4-Addition of readily available and easy-to-handle carbon nucleophlies such as organoboronic acids to electron-deficient alkenes is a useful method for efficient construction of carbon–carbon bonds. Traditionally, copper complexes have been typically employed as catalysts for 1,4-addition reactions,[1] particularly of alkyl nucleophiles such as alkylmagnesium halides,[2] dialkylzincs,[3] and trialkylaluminums.[4] Within the context of the addition of organoboronic acids, rhodium complexes have been most widely used as effective catalysts since the first report by Miyaura et al. in 1997,[5] and its asymmetric variants have also been successfully developed in the past decade.[6] In addition to rhodium complexes, palladium[7] and nickel[8] complexes have also exhibited catalytic activity in the 1,4-addition reactions of organoboronic acids and/or their derivatives. In contrast, the use of other transition metals for these useful carbon–carbon bond-forming reactions has been scarcely explored. In this context, herein we describe the development of a ruthenium-catalyzed 1,4-addition of organoboronic acids to α,β-unsaturated ketones (eq 1).[9]



(1)

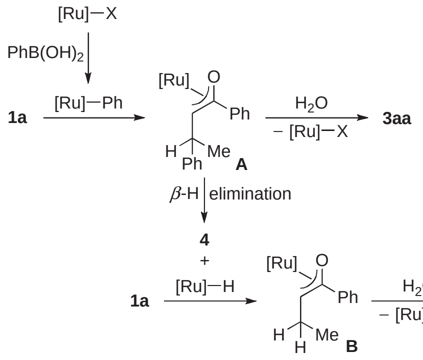
We started the study by employing 1-phenyl-2-buten-1-one (**1a**) as a model substrate and conducted reactions with phenylboronic acid (**2a**) in the presence of 5 mol % of several readily available ruthenium(II) complexes in aqueous dioxane at 90 °C. Among those examined (Table 1, Entries 1–3), $[RuCl_2(p\text{-cymene})]_2$ showed the highest catalytic activity, but it gave a mixture of 1,4-adduct **3aa** (38%), Heck-type product **4** (16%), and reduced product **5** (20%) rather nonselectively. The formation of these products can be rationalized by the pathways proposed in Scheme 1. Thus, phenylruthenium species, generated by transmetalation of phenyl group from boron to ruthenium,[9] adds to enone **1a** in a 1,4-fashion to give intermediate **A**. Protonolysis of **A** gives 1,4-adduct **3aa**, whereas β-hydride elimination of **A** produces Heck-type product **4** along with a ruthenium hydride. Hydroruthenation of this species to another molecule of **1a**, followed by protonolysis, leads to reduced product **5**. To improve the selectivity toward the formation of 1,4-adduct **3aa** by suppressing the undesired β-hydride elimination of **A**, we decided to conduct the reaction in the presence of added phosphine ligands. The use of bisphosphine ligands such as dppf did improve the selectivity toward **3aa** over **4**/**5** to some extent, but the overall reactivity became significantly lower (Entry 4). Common tertiary monophosphines such as triphenylphosphine and tricyclohexylphosphine did not show much influence on reactivity or selectivity (Entries 5 and 6). In contrast, the use of 2-(di-*tert*-butylphosphino)biphenyl[10] led to the formation of **3aa** in 70% yield by effectively minimizing the formation of **4** and **5** (Entry 7).

Table 1. Ruthenium-catalyzed 1,4-addition of phenylboronic acid (**2a**) to 1-phenyl-2-buten-1-one (**1a**)



Entry	Catalyst	Yield/%[a]		
		3aa	**4**	**5**
1	$RuCl_2(PPh_3)_3$	4	2	6
2	$[RuCp^*Cl]_4$	14	5	5
3	$[RuCl_2(p\text{-cymene})]_2$	38	16	20
4	$[RuCl_2(p\text{-cymene})]_2$/dppf	17	5	4
5	$[RuCl_2(p\text{-cymene})]_2/PPh_3$	22	17	18
6	$[RuCl_2(p\text{-cymene})]_2/PCy_3$	34	12	11
7	$[RuCl_2(p\text{-cymene})]_2/P(t\text{-Bu})_2(2\text{-PhC}_6H_4)$	70	6	7

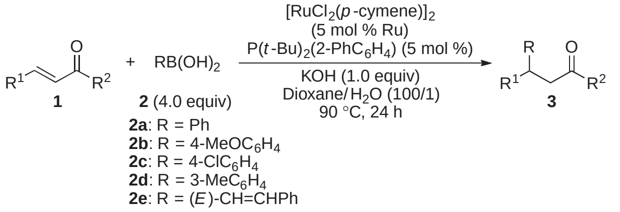
[a]Determined by ^1H NMR against internal standard ($MeNO_2$).

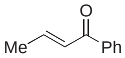
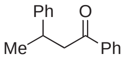
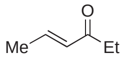
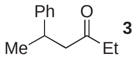
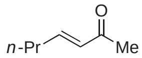
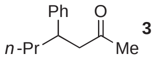
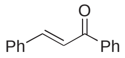
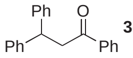
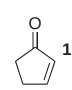
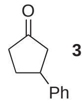
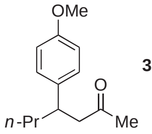
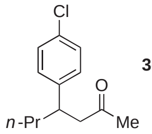
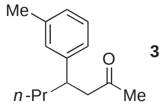
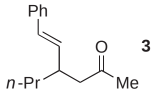


Scheme 1. Proposed reaction pathways for the formation of **3aa**, **4**, and **5**.

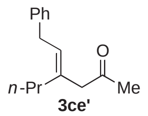
Under the conditions using $[RuCl_2(p\text{-cymene})]_2$/2-(di-*tert*-butylphosphino)biphenyl as the catalyst, several α,β-unsaturated acyclic ketones can be used for 1,4-addition of phenylboronic acid to give the corresponding products in 60–80% yield (Table 2, Entries 1–4). For cyclic ketones such as 2-cyclopenten-1-one, the reaction proceeded better without using 2-(di-*tert*-butylphosphino)biphenyl (Entry 5). With regard to the nucleophilic component, several aryl- as well as alkenylboronic

Table 2. Ruthenium-catalyzed 1,4-addition of organoboronic acids **2** to α,β-unsaturated ketones **1**: scope



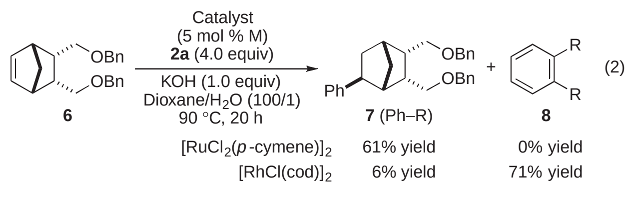
Entry	**1**	**2**	Product	Yield/%[a]
1	 **1a**	**2a**	 **3aa**	71
2	 **1b**	**2a**	 **3ba**	74
3	 **1c**	**2a**	 **3ca**	80
4	 **1d**	**2a**	 **3da**	60
5[b]	 **1e**	**2a**	 **3ea**	62
6	**1c**	**2b**	 **3cb**	82
7	**1c**	**2c**	 **3cc**	79
8	**1c**	**2d**	 **3cd**	83
9	**1c**	**2e**	 **3ce**	62[c]

[a]Isolated yield. [b]The reaction was conducted in the absence of $P(t\text{-Bu})_2(2\text{-PhC}_6H_4)$ using 3.5 equiv of $PhB(OH)_2$ and 1.5 equiv of KOH in dioxane/H_2O (27/1). [c]Containing 6% of olefin isomer **3ce′**.



3ce'

acids can be employed to give the 1,4-adducts in good yield (up to 83% yield; Entries 6–9).



It is worth noting that $[RuCl_2(p\text{-cymene})]_2$ catalyst is also effective for hydroarylation of norbornene derivatives. Thus, compound **6** undergoes hydrophenylation smoothly to give compound **7** as a sole product in 61% yield (eq 2). This result markedly contrasts to that obtained with $[RhCl(cod)]_2$ as a catalyst where one-to-two adduct **8** {R = 2,3-*endo*,*endo*-bis(benzyloxymethyl)bicyclo[2.2.1]hept-5-*exo*-yl} becomes the major product (71% yield) due to a facile 1,4-rhodium migration.[11]

In summary, we have developed a ruthenium-catalyzed 1,4-addition of organoboronic acids to α,β-unsaturated ketones. The use of 2-(di-*tert*-butylphosphino)biphenyl as the ligand in combination with $[RuCl_2(p\text{-cymene})]_2$ complex effectively catalyzes these reactions, selectively giving 1,4-adducts over Heck-type and reduced products.[12] Future studies will explore further improvement of the reaction conditions and expansion of the substrate scope as well as the development of an asymmetric variant.

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