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Cite this: DOI: 10.1039/c0xx00000x

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Ru-catalyzed 1,4-Addition of Arylboronic Acids to Acrylic Acid Derivatives in the Presence of Phenols

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[Ru(*p*-cymene)Cl₂]₂-catalyzed 1,4-addition reactions between arylboronic acids and butyl acrylate and acrylamide in the presence of phenols were investigated, good to excellent yields ¹⁰ were obtained. The addition of phenols remarkably promoted the protonolysis and inhabited the β-H elimination of the 1,4addition intermediates, and also efficiently suppressed the protonolysis of arylboronic acids.

Transition metal-catalyzed 1,4-conjugate addition of 15 organometallic reagents to α,β -unsaturated carbonyl compounds is a powerful tool for C-C bond formation reactions. ¹ Among various organometallic reagents, organoboron compounds had been extensively investigated due to their readily availability, stability and low toxicity.² 20 Since Miyaura and co-workers' pioneering work in Rhcatalyzed 1,4-addition of arylboronic acids to enones,³ the Rh(I)-^{2a,4,5} and Pd(II)-catalyzed⁶ conjugate addition has been extensively investigated and well developed. It was noteworthy that the substrates in these catalytic reactions were 25 limited to enones and enals, unsaturated esters were rarely employed as the reagents because of their easy β -H elimination.' Meanwhile, Ru(II)-catalyzed conjugate addition

- has been sporadically reported⁸ and there has been no example for the Ru(II)-catalyzed 1,4-addition of arylboronic acids to β -³⁰ unsubstituted acrylates. Herein, we report the first Ru(II)catalyzed conjugate addition of arylboronic acids to α , β -
- unsaturated esters and amides, using 2,6-di-*t*-butylphenol as a versatile additive.



 $_{35}$ Scheme 1 Competition between protonolysis and β -H elimination of the 1,4-addition intermediates

†Electronic Supplementary Information (ESI) available: Experiment details of substrates synthesis, NMR and HPLC data. See DOI: 10.1039/b000000x/

hydrolized (or protonolized) in the presence of a proton source, while complex I does not form *O*-bound intermediate II easily ¹⁰ and can undergo β -H elimination under basic conditions. $\infty \beta$ -H elimination occurs easily when the transition metal

product.9

possesses a vacant coordination site. In order to suppress the β -H elimination product, some ligands are added to prevent the metal from unsaturately coordinated. So we examined the reaction of 4-(*t*-butyl)phenylboronic acid **1a** (1.05 mmol) and

Recently, we reported a simple and efficient Ru-catalyzed 45 conjugate addition reaction of arylboronic acids to enones

under neutral conditions, in which vinyl ketones gave 1,4-

addition products with excellent yields and no β -H elimination

In transition metal-catalyzed addition reactions, it is believed

unsaturated compound into the C-M bond of an ArMX, the resulted metal complex (I) will be in equilibrium to its

enolized complex (II) (Scheme 1). When α,β -unsaturated

compounds used are ketones or aldehydes, enolization is more

55 favorable than when they are esters. Complex II can be

so that after the insertion of the C-C double bond of an α , β -

- ⁶⁵ butyl acrylate **2a** (1.0 mmol) in the presence of $[RuCl_2(p-cymene)]_2$ (2.0 mol %) in dioxane-H₂O (3.0 mL, V/V = 20:1) at 90 °C in the presence of a ligand. When PPh₃, bipyridine, and dppp were employed as the ligands, the yields of **3aa** were 43%, 0%, and 0%, respectively. In the presence of PPh₃
- ⁷⁰ and DPPP as ligands, protonolysis product of *t*-butylphenylboronic acid was the major byproduct. We also tried organic acids as additives, hoping that the presence of an acid to stimulate the protonolysis of the enolate of the 1,4-addition intermediate (**II** in scheme 1). As a result, in the ⁷⁵ presence of 10 mol% of benzoic acid, the yield was 57% together with some *t*-butylbenzene; while in the presence of 20 mol% of acetic acid, the yield decreased to 12% with the generation of a large amount of *t*-butylbenzene (70%) as the byproduct. Apparently, the protonolysis of arylboronic acid
- ⁸⁰ becomes more favorable under acidic conditions. However, the β -H elimination became overwhelming even in the presence of a weak base, as a result, addition of 10 mol% of NaOAc to the reaction, no desired 1,4-addition product was detected; only Heck-type product was obtained.
- ⁸⁵ Because both oxygen-based ligands and the acidity of the reaction condition play a crucial role in controlling the protonolysis of arylboronic acids and the β -H elimination process,¹¹ neutral or weak acidic oxygen-based ligand, such as

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widely-used pentane-2,4-dione and rarely-used phenols, were tested. When pentane-2,4-dione was used as ligand, the reaction gave 3aa in only 20% yield, most of 1a and 2a was remained (Table 1, entry 7). When phenol was used as the 5 ligand in our catalytic system, the reaction produced 1,4addition product 3aa in 90% yield (Table 1, entry 8). Other phenols were also tested, and 2,6-di(t-butyl)phenol performs best (For more details, see supporting information, Table 1). This result prompted us to explore the possibility of using 10 oxygen-based ruthenium complexes as catalysts for the 1,4addition reaction. As a result, if the catalyst was pre-formed with $[Ru(p-cymene)Cl_2]_2$ and 1 to 2 equivalents of PhONa, the reaction gave 1,4-addition product in not more than 30% yield together with varying amount of Heck-type product. 15 Replacing the catalyst with [Ru(benzene)Cl₂]₂, the yield was decreased from 94% to 85% (Table 1, entry 10 vs entry 11); other ruthenium catalysts are inefficient, [Ru(COD)Cl₂]_n and RuCl₃.xH₂O are totally inert (Table 1, entries 13 and 14). This reaction was not susceptible to the temperature, when the 20 reaction was carried out at 120 °C, the yield was almost equal to that at 90 °C; while at 50 °C the yield was slightly decreased even with longer reaction time. Other solvents, such as THF, acetone, toluene, methanol and DMF, decreased the yields with varying degrees in our catalytic system. If the 25 reaction was carried out in a dry solvent, the yield was

remarkably decreased (See supporting information, Table 1). On the basis of these optimization studies, we employed [RuCl₂(p-cymene)]₂ (2 mol %) as the catalyst, 2,6-di-(tbutyl)phenol (10 mol %) as the additive, in dioxane/H₂O = 20 30 : 1 (V/V), 90 °C and 12 h as the standard reaction conditions for the following catalytic conjugate addition reactions.

Table 1 Ru-catalyzed 1,4-addition reaction of 1a and 2a 0

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B OH + Catalyst							
OBu-n Solvent t-Bu OBu-n							
t-Bu 2a		3aa					
Entry	Catalyst	Additive	$\frac{1}{1}$ Vield $(\%)^{b}$				
1	[RuCl ₂ (<i>n</i> -cymene)] ₂	None	75 ^c				
2	$[RuCl_2(p \text{ cymene})]_2$	PPh ₂	43				
3	$[RuCl_2(p \text{ cymene})]_2$	Bipyridine	ND				
4	$[RuCl_2(p - cymene)]_2$	DPPP	ND				
5	$[RuCl_2(p-cymene)]_2$	Benzoic acid	57				
6	$[RuCl_2(p-cymene)]_2$	HOAc	12				
7	$[RuCl_2(p-cymene)]_2$	Pentane-2,4-dione	20				
8	$[RuCl_2(p-cymene)]_2$	Phenol	90				
9	[RuCl ₂ (<i>p</i> -cymene)] ₂	2,6-Dimethylphenol	92				
10	[RuCl ₂ (<i>p</i> -cymene)] ₂	2,6-Di-t-butylphenol	94				
11	[Ru(benzene)Cl ₂] ₂	2,6-Di-t-butylphenol	85				
12	RuCl ₂ (PPh ₃) ₃	2,6-Di-t-butylphenol	ND				
13	[RuCl ₂ (COD)] _n	2,6-Di-t-butylphenol	ND				
14	RuCl ₃ ·xH ₂ O	2,6-Di-t-butylphenol	ND				
^{<i>a</i>} All the reactions were carried out with $1 (1.05 \text{ mmol}), 2 (1.00 \text{ mmol})$,							
ruthenium complex (2.0 mol %) and an additive (10 mol%) in a mixed							
solvent [dioxane/H ₂ O = 20/1 (v/v), 3 mL] at 90 °C under N ₂ for 12 h.							
^b Yields were determined by GC (signal-integration method with							
durene as an internal standard, Heck-type product was less than 2%).							
^c With 20% of Heck-type product. ^d ND: not detected.							

35 Under the optimized reaction conditions, a wide range of arylboronic acids and acrylates or acrylamides were

investigated. The results are summarized in Table 2. The para- and meta- substituted arylboronic acids 1c-o can efficiently react with 2a to afford the corresponding addition 40 products in good to excellent yields (Table 2). The catalytic reactions tolerated various functional groups, such as OCF₃, Cl, F, Br, COCH₃, CO₂CH₃ and CHO on the phenyl rings of arylboronic acids 1. These results indicate that the catalytic reaction is not sensitive to the electronic properties of the 45 substituent, but it is susceptible to the position of the substituents on the phenyl rings. For example, 3methylphenylboronic acid (1c) afforded 3ca in 85% yield (Table 2, entry 3) whereas 2-methylphenylboronic acid (1b) gave 3ba in only 35% yield even if 2.5 eq. of 1b was used 50 (Table 2, entry 2). As mentioned before, this reaction is sensitive to the acidity of the reaction condition, when acrylic acid as substrate, almost all of the arylboronic acids were protonolyzed. Likewise, the catalytic reaction is very sensitive to the steric hindrance with the alkenes 2, no reaction took 55 place with α - or β -substituted acrylic substrates under the standard reaction conditions.

Table 2 Ru-catalyzed 1,4-addition reaction of arylboronic acids 1 with alkenes 2^a

ArB(OH) ₂	+ ⁄⁄ E -	[RuCl ₂ (p-cyi 2,6-di- <i>t</i> -but solvent,	mene)] ₂ ylpheno , 90°C	2 D I	Ar		
1	2a: E = CO ₂ B 2b: E = CONH 2c: E = CN	u-n 1 ₂			3		
Entry	Ar	F	3	Product	$\text{Yield}^{b}(\%)$		
1	p-t-BuC ₆ H ₄ (1a) 2	a	3aa	94		
2	$o-MeC_6H_4$ (1b)	2	la	3ba	30^{c}		
3	m-MeC ₆ H ₄ (1c)	2	a	3ca	85		
4	p-MeC ₆ H ₄ (1d)	2	a	3da	88		
5	$C_{6}H_{5}(1e)$	2	la	3ea	91		
6	p-FC ₆ H ₄ (1f)	2	la	3fa	86		
7	$p-CF_{3}C_{6}H_{4}(1g)$	2	a	3ga	90		
8	p-ClC ₆ H ₄ (1h)	2	la	3ha	92		
9	p-CF ₃ OC ₆ H ₄ (1	i) 2	la	3ia	88		
10	<i>p</i> -CH ₃ OC ₆ H ₄ (1	.j) 2	la	3ja	84		
11	p-BrC ₆ H ₄ (1k)	2	la	3ka	74		
12	p-CH ₃ COC ₆ H ₄	(1I) 2	la	3la	90		
13	p-CO ₂ CH ₃ C ₆ H ₄	(1m) 2	la	3ma	87		
14	<i>p</i> -CHOC ₆ H ₄ (1)	n) 2	a	3na	81		
15	m-CHOC ₆ H ₄ (1	o) 2	a	3oa	83		
16	$C_{6}H_{5}(1e)$	2	b	3eb	58		
17	$C_{6}H_{5}(1e)$	2	c	3ec	ND		
^a All the reactions were carried out with 1 (1.0 mmol), 2 (1.0 mmol),							
ruthenium complex (2.0 mol %), 2,6-di-t-butylphenol (10.0 mol %), in							
dioxane/water = 20 : 1 (v/v) (3 mL) at 90 °C under N ₂ for 12 h. ^{<i>b</i>} Isolated							
vield (Heck-type product is less than 3%). ² 2.5 eq. of aryboronic acid							

was used.

It is still a puzzle what the role phenols play in the catalytic 1,4-addition reaction, but it is clear that phenols do not serve only as ligands, as depicted earlier that the pre-formed catalyst from [Ru(cymene)Cl₂]₂ and varying amounts of 65 NaOPh performed worse than [Ru(cymene)Cl₂]₂ and phenol. Further experiments showed that phenols do not only serve as a pH adjusting agent either. If the reaction was run in buffered solutions (citric acid/sodium hydroxide, potassium dihydrogen phosphate/disodium hydrogen phosphate, and sodium 70 tetraborate/hydrochloric acid) with a pH varying from 5.0 to 9.0, the yields varying from 78% to 31% acompanying with Chemical Communications Accepted Manuscrip

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protonolysis product of arylboronic acid and Heck-type product. It is evident that the 1,4-addition reaction also involves transmetallation, insertion of the C=C double bond of acrylate to C-Ru bond, and the protonolysis steps as

- ⁵ proposed in the literature.¹² The bulkiness of the catalyst and the right acidity and coordinating ability of the phenols may work jointly to facilitate the enolization and protonolysis of the enolized intermediate as depicted in Scheme 1.
- In summary, we have developed a straightforward and ¹⁰ efficient Ru-catalyzed 1,4-addition reactions of organoboronic acids to acrylates and acryamide. It is noteworthy that the use of phenols as additives efficiently suppressed the β -hydride elimination products, and the protonolysis and self-coupling of the arylboronic acids. As a result, only one equivalent ¹⁵ arylboronic acids was used, the acrylates can still efficiently undergo full conversion.

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