

Ruthenium-catalyzed coupling of aldimines with arylboronates: new synthetic method for aromatic ketones†

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Using the chelation strategy, the reaction of aldimines bearing the 3-picolin-2-yl group with various arylboronates in the presence of a ruthenium catalyst furnished the corresponding ketimines in high yields for a short reaction time; the resulting ketimines were readily converted to ketones by hydrolysis.

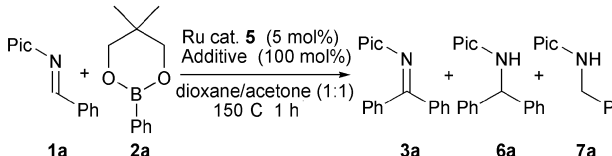
The transition metal-catalyzed reactions involving a C–H bond cleavage have opened up a new methodology for the addition of relatively inert C–H bonds to C–C multiple bonds.¹ In particular, the chelation-assisted hydroacylation of 1-alkene or alkyne is one of the most promising ways for transforming aldehydes to ketones in which the resulting ketones are aryl-alkyl or alkyl-alkyl ketones.² However, direct synthesis of aryl-aryl ketone from aldehydes (or corresponding imines) has been rarely developed. One of the more notable direct syntheses of aryl-aryl ketones (as reported by Suggs *et al.*) is the stoichiometric reaction of the iminoacylrhodium(III)-hydride complex with benzoyl chloride yielding diphenyl ketimine.³ Relevant catalytic approaches are the Heck type reaction between aldehydes (or aldimines) and aryl-metal species generated from oxidative addition of aryl halide to transition metals,⁴ or the reaction of α,β -unsaturated aldehydes with boronic acids.^{5,6} Here we wish to report the ruthenium-catalyzed coupling of aldimines with arylboronates for the synthesis of aromatic ketimines, which form ketones upon hydrolysis (Scheme 1).

In our initial experiments, when the reaction of **1a** (R = Ph) with **2a** (Ar = Ph) was carried out in the presence of 5 mol% $\text{Ru}_3(\text{CO})_{12}$ (**5**)⁷ in acetone–1,4-dioxane solvent mixture (w/w = 1 : 1) at 150 °C for 1 h, ketimine of benzophenone (**3a**) was obtained in a 61% yield along with **6a** (13%) and **7a** (22%), determined by GC (Table 1, entry 1).⁸ Attempts to avoid the formation of **6a** and **7a**, reduced forms of **1a** and **3a**, have failed under various reaction conditions.⁹ However, addition of methyl vinyl ketone (MVK) dramatically suppressed the formation of **6a** and **7a** without affecting the yield of **3a** (entry 3). Other olefins such as cyclohexene

or 1-cyclohexenone were ineffective in suppressing the formation of **6a** and **7a**.

With these observations at hand, we investigated the scope of the coupling reactions of **1** and **2** (Table 2).[‡] The electronic effect of the 4-substituent in **1** and **2** had no significant influence on reactivity, and the corresponding diaryl ketones were obtained in good yields after hydrolysis in most cases except for **2d** (entries

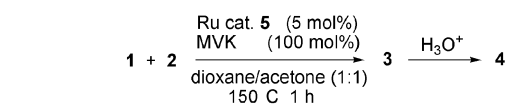
Table 1 Additive effects on the Ru-catalyzed coupling of **1a** with **2a**^a



Entry	Additives	Yield ^b (%) of		
		3a	6a	7a
1	none	61	13	22
2	cyclohexene	63	13	24
3	methyl vinyl ketone ^c	94	4	1
4	1-cyclohexenone	83	10	5

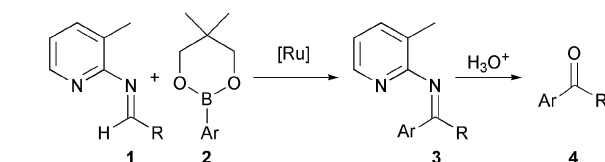
^a Reaction conditions: **1a** (0.216 mmol), 1.2 equiv. of **2a**, 5 mol% **5**, 100 mol% additive, 0.2 ml solvent mixture at 150 °C (bath temp.) for 1 hour. ^b Determined by GC based on **1a**. ^c Small amount of addition product of MVK with **2a** (< 4%) was also observed. Pic = 3-picolin-2-yl.

Table 2 Scope of the Ru-catalyzed coupling of **1** with **2**^{a,b}



Entry	R of 1	Ar of 2	Isolated yield ^c (%) of 4
1	Ph (1a)	Ph (2a)	85 (94) (4aa)
2	1a	4-MeOC ₆ H ₄ (2b)	82 (91) (4ab)
3	1a	4-MeC ₆ H ₄ (2c)	75 (86) (4ac)
4	1a	2-MeC ₆ H ₄ (2d)	18 (28) (4ad)
5	1a	4-FC ₆ H ₄ (2e)	86 (93) (4ae)
6	1a	4-ClC ₆ H ₄ (2f)	84 (96) (4af)
7	1a	3-ClC ₆ H ₄ (2g)	86 (94) (4ag)
8	1a	4-BrC ₆ H ₄ (2h)	74 (88) (4ah)
9	4-MeOC ₆ H ₄ (1b)	2b	71 (86) (4bb)
10	4-CF ₃ C ₆ H ₄ (1c)	2b	88 (94) (4cb)

^a Reaction conditions: **1** (0.216 mmol), 1.2 equiv. of **2**, 5 mol% **5**, 1 equiv. of MVK, 0.2 ml solvent mixture at 150 °C (bath temp.) for 1 hour. ^b Small amounts of **6** (< 4%), **7** (< 2%) and addition product of MVK with **2** (< 4%) were also observed before hydrolysis. ^c GC yield of **3** based on **1** is given in parentheses.



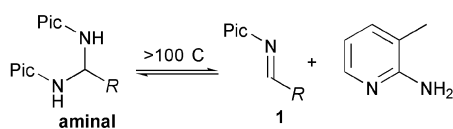
Scheme 1

† Electronic supplementary information (ESI) available: characterization of new compounds. See <http://www.rsc.org/suppdata/cc/b4/b415810e/> *junch@yonsei.ac.kr

1–10). The reaction of **2d** with **1a** was sluggish, probably owing to the unfavourable steric interaction (entry 4). For the coupling of aliphatic aldimine with **2**, aminal was used as an imine precursor of aliphatic aldehyde, in which aldimine **1** and 2-amino-3-picoline is dissociated from aminal above 100 °C (Scheme 2).¹⁰ When the reaction of aminal with **2** was carried out, it was found that secondary as well as primary alkyl aminals gave the corresponding ketone in moderate yields irrespective of the electronic effect of the 4-substituent in **2** (Table 3).

From the mechanistic point of view, the following mechanism can be suggested for the direct addition of aryl–metal species to imine followed by β -hydrogen elimination (Scheme 3).^{4(b)–(d),6,11}

Alternatively, as far as aldimines of 2-amino-3-picoline are concerned,¹² the chelation-assisted C–H bond cleavage of **1** by **5** might take place. Thus we have a preference for the following mechanism for the coupling reaction of **1** with **2**, though other reaction pathways cannot be ruled out (Scheme 4). The first step might be an oxidative addition of the C–H bond in **1** into the

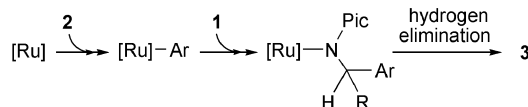


Scheme 2

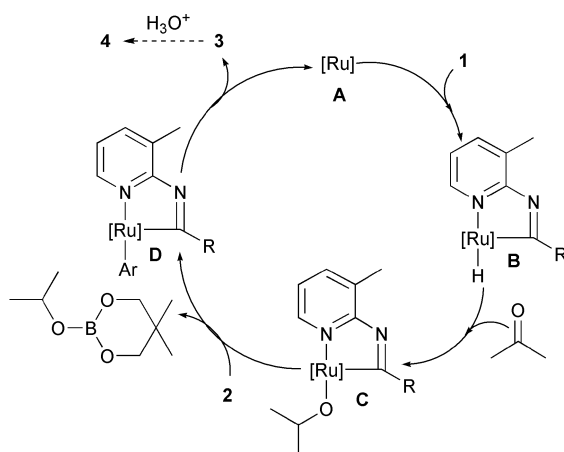
Table 3 Scope of the Ru-catalyzed coupling of aminal with **2**^a

Entry	R of aminal	2	Isolated yield (%) of 4
1	<i>n</i> -C ₅ H ₁₁ (1d)	2b	47 (58) (4db)
2	1d	2e	46 (60) (4de)
3	Cy (1e)	2b	55 (67) (4eb)
4	1e	2e	51 (60) (4ee)

^a Same as in Table 2: aminal (0.216 mmol) was used instead of **1**.



Scheme 3

Scheme 4 Proposed mechanism for the coupling of **1** with **2**.

ruthenium metal center yielding the iminoacylruthenium(II)-hydride species (**B**).¹² A hydride attack of **B** on acetone leads to the isopropoxy iminoacyl ruthenium(II) species (**C**). Transmetalation of **C** with **2** gives the iminoacylruthenium(II)-aryl species (**D**).¹³ And subsequent reductive elimination of **D** furnishes ketimine **3**, which is hydrolyzed by H₂O to give the corresponding ketone **4**.

In summary, we developed the coupling reaction of aldimines with arylboronates using the chelation protocol. This transformation represents a new catalytic reaction for the synthesis of aromatic ketones. More detailed mechanistic studies and improved applications are under way.

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Notes and references

‡ **Representative Procedure:** A screw-capped pressure vial (1 mL) was charged with 0.216 mmol of **1**, 6.9 mg (0.0108 mmol) of Ru₃(CO)₁₂ (**5**), 0.259 mmol of **2** and 15.1 mg (0.216 mmol) of methyl vinyl ketone and the reaction mixture was dissolved in 0.2 mL of a 1,4-dioxane–acetone mixture (w/w = 1 : 1). It was stirred in an oil bath that was preheated to 150 °C for 1 h. After the reaction, the resulting mixture was hydrolyzed using 10 mL of 1 M HCl and THF mixture solution for 12 h and then purified by column chromatography (SiO₂, *n*-hexane : ethyl ether = 10 : 1) to afford the corresponding ketones.

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- Other catalysts such as Rh(PPh₃)₃Cl, Ru(PPh₃)₃Cl₂, RuHCl(CO)(PPh₃)₃, Pd(OAc)₂ and Pd(PPh₃)₂Cl were ineffective except for RuH₂(CO)(PPh₃)₃, albeit in low yield (57% GC yield) as compared with **5**.
- (a) The direct conversion of aldehydes to ketones using the chelation-assisted catalytic system of **5** and 2-amino-3-picoline (*in situ* generation of the aldimine) was unsuccessful, because 2-amino-3-picoline is supposed to react with **5** to give an inactive complex during the reaction, see: J. A. Cabeza, *Eur. J. Inorg. Chem.*, 2002, 1559; (b) In the absence of acetone, the yield of **3a** was decreased (47% GC yield) and severe reduction of **1a** also took place; (c) Boronic acids were also

applicable, but yields were approximately 20% lower compared with those of **2**.

- 9 When only **1a** was stirred in dioxane–acetone mixture with **5** (5 mol%) at 150 °C for 1 hour, **7a**, a reduced form of **1a**, was observed in 25% GC yield. One of the possible explanations for the formation of these reduced forms of **1** and **3** may be a water-gas shift reaction producing molecular hydrogen, H₂. However, we observed comparable results even under anhydrous conditions. For a similar observation, see: ref. 4(b).
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