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Tandem Catalysis: Access to Ketones from Aldehydes and Arylboronic Acids *via* Rhodium-Catalyzed Addition/Oxidation

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Abstract: Direct cross-coupling reactions of aromatic aldehydes with arylboronic acids afforded ketones in high yields and under mild conditions in the presence of a rhodium catalyst, acetone and a base. This new reaction, involving a formal aldehyde C–H bond activation, is believed to proceed *via* a tandem process involving addition of the organometallic species to the aldehyde followed by oxidation by β-hydride transfer.

Keywords: aldehydes; boronic acids; homogeneous catalysis; ketones; rhodium

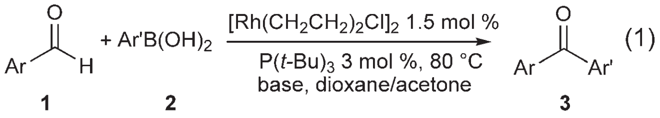
Introduction

Benzophenone frameworks, a structural unit encountered in numerous natural products,[1] are generally constructed by Friedel–Craft reaction or by addition of arylmagnesium or lithium reagents to aryl aldehydes followed by oxidation. In the first approach, the generation of large amounts of salts, originating from the Lewis acid and regioselectivity problems, giving rise to mixture of isomers, generally results in tedious purifications. In the second one, yields are generally moderate and intramolecular variations have been utilized to enhance the overall process. Moreover, this approach requires stoichiometric amounts of oxidant.

A green process to access this framework *via* tandem reactions[2] involving catalytic addition to the aldehyde and catalytic oxidation would be highly desirable. Examples of such processes are rare and involve oxidative addition of aryl halides to low-valent transition metals followed by reaction with aldehydes or aldimines (insertion and β-hydride elimination mechanism).[3] However, a high temperature is generally needed under basic[3b] or reductive conditions[3c] preventing the use of functionalized substrates. Furthermore, yields are generally moderate or limited with respect to substrate tolerance.[3a]

Results and Discussion

We report here the first catalytic cross-coupling reaction of arylboronic acids with aryl aldehydes to afford diaryl ketones *via* a tandem catalytic process involving addition and oxidation *via* β-hydride transfer [Eq. (1)] under very mild conditions.

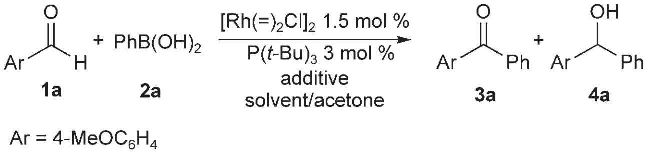


1 2 3 (1)

We recently reported[4] a direct access to ketones from aldehydes under rhodium catalysis in the presence of potassium aryltrifluoroborates.[5] In order to improve the scope of the reaction, we wondered if the readily available arylboronic acids would participate in this reaction.[6] Unfortunately, under the previous conditions that used $[Rh(CH_2CH_2)_2Cl]_2$ and tri-*tert*-butylphosphane, in the binary solvent system dioxane/acetone, the reaction of phenylboronic acid **2a** with 4-methoxybenzaldehyde **1a** only afforded the carbinol derivative **4a**[5g,7] and not the expected ketone **3a** (Table 1).

In order to achieve exclusive formation of the benzophenone adduct, several additives were evaluated. In the presence of acids, no reaction was observed, but the addition of bases was found to be crucial for the formation of the expected ketone at the expense

Table 1. Optimization of the rhodium-catalyzed formation of diaryl ketones from aldehydes and arylboronic acids.[a]



Entry	Base (equivs.)	Conversion	Time [h]	**3a**/**4a**
1	None	40	24	0/100
2	$KHCO_3$ (2)	6	24	57/43
3	KOH (2)	0	24	
4	NEt_3 (2)	0	24	
5	K_2CO_3 (2)	76	4	100/0
6	K_2CO_3 (1)	72	8	100/0
7	K_2CO_3 (3)	74	4	100/0
8[b]	K_2CO_3 (2)	100	4	0/0[c]
9[d]	K_2CO_3 (2)	50	4	70/30
10[e]	K_2CO_3 (2)	20	24	10/90
11[f]	K_2CO_3 (2)	100	3	0/100

[a] Reactions conducted using 0.5 mmol of **1a**, 2 equivs. of **2a**, an additive, with 1.5 mol% of $[Rh(CH_2CH_2)Cl]_2$ and 3 mol% $P(t\text{-}Bu)_3$ at 80 °C in 2.5 mL 1,4-dioxane/acetone 4:1.

[b] Reaction in EtOH/acetone, 4:1.

[c] Exclusive formation of aldolization-crotonization adduct 4-(4-methoxyphenyl)-but-3-en-2-one.

[d] Reaction conducted at 60 °C.

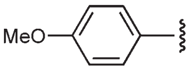
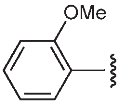
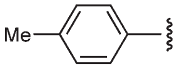
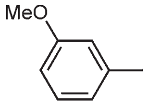
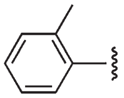
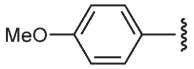
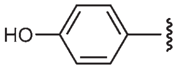
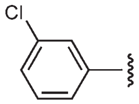
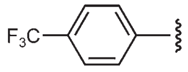
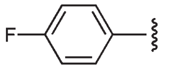
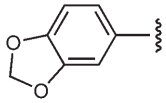
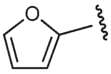
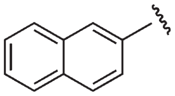
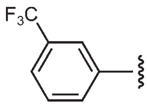
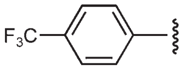
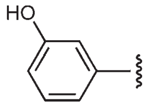
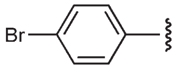
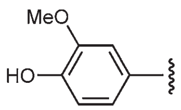
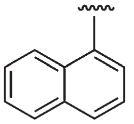
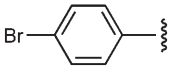
[e] Reaction conducted at 40 °C.

[f] 30 min at room temperature then 80 °C.

of carbinol (entries 2–7). Among the tested bases, potassium carbonate was found to be the most suitable, affording a quantitative conversion in benzophenone **3a** as the sole product upon reaction of **1a** with **2a** (entries 5–7). The amount of base did not appear to be crucial, but the fastest reaction rates were achieved using two equivalents of base compared to aldehyde (entry 5). Among the solvent systems tested, a mixture of dioxane/acetone appeared to be the most suitable and clean conversion to ketone was only possible at a temperature above 80 °C. In may other polar or protic solvents (see, for example, entry 8), aldehyde **1a** was completely consumed but we observed only the formation of the aldolization-crotonization product in quantitative yield: 4-(4-methoxyphenyl)-but-3-en-2-one. On the contrary, in dioxane, no trace of this by-product was detected by GC/MS. The reaction temperature has also a crucial role under these conditions: lowering the temperature below 80 °C resulted in a decrease of ketone formation at the expense of carbinol (entries 9 and 10). Finally, we found that stirring the reaction mixture for 30 min at room temperature before heating at 80 °C had a beneficial effect on the conversion to ketone **3a** (entry 11).

Indeed, under these optimized conditions, reaction of **1a** with **2a** using $[Rh(CH_2CH_2)_2Cl]_2$ in conjunction

Table 2. Rhodium-catalyzed formation of diaryl ketones from aldehydes and arylboronic acids.[a]

Entry	Ar	Ar′	Yield[b] [%]
1	**1a** 	**2a** Ph	92
2	**1b** 	**2a**	73
3	**1c** 	**2b** 	64
4	**1a**	**2c** 	65
5	**1a**	**2d** 	74
6	**1d** 	**2d**	82
7	**1d**	**2e** 	85
8	**1d**	**2f** 	65
9	**1d**	**2g** 	84
10	**1e** 	**2g**	95
11	**1f** 	**2h** 	95
12	**1f**	**2i** 	52
13	**1g** 	**2d**	70
14	**1h** 	**2j** 	93
15	**1i** 	**2k** 	92
16	**1j** 	**2d**	52

[a] Reactions conducted using 0.5 mmol of **1**, 2 equivs. of **2**, 2 equivs. of K_2CO_3 with 1.5 mol% of $[Rh(CH_2CH_2)Cl]_2$ and 3 mol% $P(t\text{-}Bu)_3$ at 80 °C in 2.5 mL 1,4-dioxane/acetone 4:1.

[b] Isolated yields of ketone.

with the P(t-Bu)$_3$ ligand[8] as catalyst afforded a 92% yield of ketone **3a** at 80 °C, using a binary mixture of dioxane/acetone as solvent and K_2CO_3 as base (Table 2, entry 1).

These conditions proved to be general and a great variety of ketones were obtained from the reaction of aromatic aldehydes with arylboronic acids. Good to excellent yields were generally achieved with many substitution patterns on the reaction partners. It appeared that the electronic nature on the organoboron reagent did not have a great influence as similar yields and reaction rates were obtained with boronic acids bearing either electron-withdrawing or -donating substituents (entries 6 and 8). Yields were generally higher with electron-rich arylaldehydes but comparable yields were generally observed.

More specifically, acidic hydroxy substituents on the aromatic ring were tolerated in this reaction, preventing tedious protection/deprotection sequences (entries 6–9, 14 and 15). This result is all the more surprising, as, under these basic conditions, deprotonation of the phenol should result in an increased electron density in the aldehyde function, diminishing its electrophily. This result may suggest that insertion of the aldehyde into the aryl-rhodium species is not the rate-determining step of the whole process. Noteworthy, this reaction also allowed access to *ortho*-substituted benzophenones in high yields (entries 2, 4 and 15). Under these conditions, reactions of aliphatic aldehydes with arylboronic acids only led to traces of the expected ketone.

In order to get some insight into the reaction mechanism, the reaction of aldehyde **1a** and boronic acid **2a** was monitored by GC/MS under optimized conditions (Figure 1). To our surprise, and contrary to the reaction profile obtained with potassium aryltrifluoroborates, we observed fast disappearance of the aldehyde with concomitant initial formation of the carbinol and not the ketone. Thereafter, the alcohol is slowly transformed to ketone.

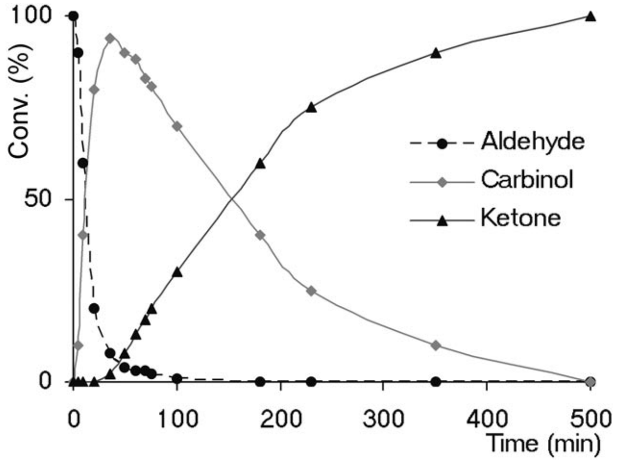
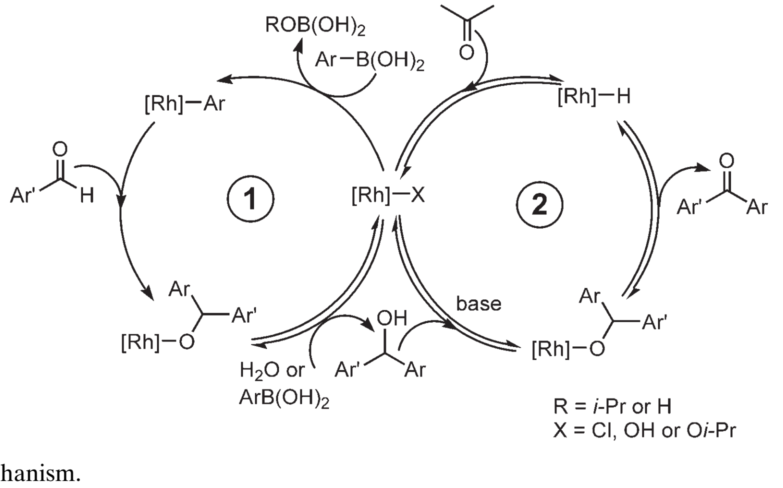


Figure 1. Reaction profile in the addition of **2a** to **1a**.

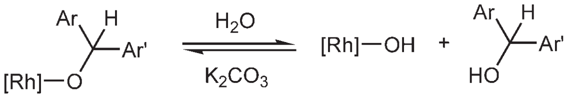
Indeed, it appeared that two consecutive catalytic reactions are occurring under these conditions: addition of the boronic acid to aldehydes to produce the carbinol and oxidation of the resulting alcohol to the ketone. The results were confirmed by the fact that in the absence of base, only carbinol was formed in quantitative yields, as already demonstrated by Miyaura et al.[7d] Similarly to potassium organotrifluoroborates, the presence of acetone as co-solvent was found to be crucial for the process; diarylcarbinols being obtained in quantitative yields in its absence. From these results, the overall mechanism is believed to involve a tandem process including rhodium-catalyzed addition of boronic acid to aldehydes (Scheme 1, cycle 1) followed by slow oxidation of the resulting carbinol *via* β-hydride transfer (cycle 2).

Indeed transmetallation of the organometallic reagent to the rhodium(I) complex followed by the insertion of the aldehyde into the aryl-rhodium(I) furnishes an alkoxo-rhodium species. It is known that boronic acids are prone to dehydratation, resulting in the formation of boroxine and water.[9] Indeed, the in-



Scheme 1. Postulated mechanism.

itial formation of the carbinol is explained by protonation of this alkoxo-rhodium intermediate by the water formed in the reaction medium (or directly by the boronic acid), giving an active hydroxo-rhodium species. Transmetallations of organoboron compounds to alkoxo or hydroxo complexes of palladium,[10] rhodium[11] or ruthenium[12] have been described, allowing regeneration of the aryl-metal species. We believe that the role of the base is the regeneration of an alkoxo-rhodium compound[13] [Eq. (2)], initiating the second catalytic cycle. β-Hydride elimination from the generated alkoxo-rhodium(I) complex[14] would release the diaryl ketone and a rhodium(I) hydride species.



(2)

The latter reacts with acetone to afford an alkoxo-rhodium(I) complex which is suitable for transmetallation with the boron reagent.[4]

Conclusions

Thus, we have described the cross-coupling reaction of organoboronic acids with aldehydes to access directly ketones under mild conditions *via* formal C–H bond *activation*. This efficient reaction is believed to occur through a tandem process involving an addition mechanism followed by an unusual oxidation *via* hydrogen transfer, with inexpensive acetone playing the part of hydride acceptor.

Experimental Section

Typical Procedure for Carbonylation of Arylboronic acids: Preparation of Benzo[1,3]dioxol-5-yl-(4-fluorophenyl)methanone (Entry 10)

To a mixture of 4-fluorophenylboronic acid **2g** (1 mmol, 140 mg), potassium carbonate (138 mg, 2 equivs.), chlorobis(ethylene)rhodium(I) dimer (7.5 μmol, 2.9 mg) and piperonal **1e** (0.5 mmol, 75 mg) in degassed dioxane (2 mL) was added a solution of tri-*tert*-butylphosphane in degassed toluene (15 μmol, 3 M solution, 50 μL) followed by degassed acetone (0.5 mL) under an argon atmosphere. After 30 min stirring at room temperature, the flask was placed in a preheated oil bath at 80 °C. The mixture was stirred until completion of the reaction (followed by GC analysis). After concentration under reduced pressure, the crude mixture was purified by silica gel chromatography to afford the analytically pure ketone as a white solid; yield: 115.5 mg (85 %). CG: R_t = 12.2 min; mp 104 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.08 (2H, s), 6.88 (1H, dd, J = 1.4 Hz and 7.4 Hz), 7.16 (1H, t app, $J_{H,H}$ = $J_{H,F}$ = 8.7 Hz), 7.33 (1H, s), 7.35 (1H, dd, J = 7.4 Hz and 1.7 Hz), 7.79 (2H, dd, $J_{H,H}$ = 8.7 Hz and $J_{H,F}$ = 5.4 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 101.9, 107.7, 109.8, 115.4 (d, $J_{C,F}$ = 22 Hz), 126.6, 131.8, 132.3 (d, $J_{C,F}$ = 9 Hz), 134.3, 148.0, 151.6, 165.1 (d, $J_{C,F}$ = 252 Hz), 193.7; MS (IE, 70 eV): m/z = 244 (M$^+$, 73 %), 149 (100 %), 123 (36 %), 95 (29 %); HRMS: m/z = 245.0607, calcd. for $C_{14}H_{10}O_3F$: 245.0614.

In the case of hydroxy substituted arenes, the crude reaction mixture was acidified with 10 % aqueous HCl, the aqueous phase extracted 3 times with CH_2Cl_2, the organic phases dried over $MgSO_4$ and concentrated.

Acknowledgements

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References

[1] For some examples see: a) J. W. Lampe, C. K. Biggers, J. M. Defauw, R. J. Foglegong, S. E. Hall, J. M. Heerding, S. P. Hollinhead, H. Hu, P. F. Hughes, G. E. Jagdmann, M. G. Johnson, Y.-S. Lai, C. T. Lowden, M. P. Lynch, J. S. Mendoza, M. M. Murphy, J. W. Wilson, L. M. Ballas, K. Carter, J. W. Darges, J. E. Davis, F. R. Hubbard, M. L. Stamper, *J. Med. Chem.* **2002**, *45*, 2624; b) T. Katoh, O. Ohmori, K. Iwasaki, M. Inoue, *Tetrahedron* **2002**, *58*, 1289; c) F. Kaiser, L. Schwink, J. Velder, H.-G. Schmalz, *Tetrahedron* **2003**, *59*, 3201; d) D. Iijima, D. Tanaka, T. Ogamino, Y. Ishikawa, S. Nishiyama, *Tetrahedron Lett.* **2004**, *45*, 5469; e) C. Zhang, J. G. Ondeyka, K. B. Herath, Z. Guan, J. Collado, G. Platas, F. Pelaez, P. S. Leavitt, A. Gurnett, B. Nare, P. Liberator, S. B. Singh, *J. Nat. Prod.* **2005**, *98*, 611.

[2] Reviews: a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115; b) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* **2003**, 551; c) D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365; d) H.-C. Guo, J.-A. Ma, *Angew. Chem. Int. Ed.* **2005**, *44*, 2.

[3] a) T. Satoh, T. Itaya, M. Miura, M. Nomura, *Chem. Lett.* **1996**, 823; b) T. Ishiyama, J. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 12043; c) Y.-C. Huang, K. K. Majumdar, C.-H. Cheng, *J. Org. Chem.* **2002**, *67*, 1682.

[4] M. Pucheault, S. Darses, J.-P. Genet, *J. Am. Chem. Soc.* **2004**, *126*, 15356.

[5] For a rerview of rhodium-catalyzed processes involving potassium organotrifluroborates, see: S. Darses, J.-P. Genet, *Eur. J. Org. Chem.* **2003**, 4313; see also: a) M. Pucheault, S. Darses, J.-P. Genet, *Eur. J. Org. Chem.* **2002**, 3552; b) M. Pucheault, S. Darses, J.-P. Genet, *Tetrahedron Lett.* **2004**, *45*, 4729; c) L. Navarre, S. Darses, J.-P. Genet, *Chem. Commun.* **2004**, 1108; d) L. Navarre, S. Darses, J.-P. Genet, *Eur. J. Org. Chem.* **2004**, 69; e) L. Navarre, S. Darses, J.-P. Genet, *Angew. Chem.* **2004**, *116*, 737; *Angew. Chem. Int. Ed.* **2004**, *43*, 719; ; f) M. Pucheault, S. Darses, J.-P. Genet, *Chem. Commun.* **2005**, 4714; g) L. Navarre, S. Darses, J.-P. Genet, *Adv. Synth Catal.* **2006**, *348*, 317.

[6] For direct coupling of cinnamaldehydes with arylboronic acids under Rh catalysis with concomitant C=C reduction, see: Z. Wang, G. Zou, J. Tang, *Chem. Commun.* **2004**, 1192.

[7] a) S. Oi, M. Moro, Y. Inoue, *Chem. Commun.* **1997**, 1621; b) M. Sakai, M. Ueda, N. Miyaura, *Angew. Chem. Int. Ed.* **1998**, *37,* 3279; c) R. A. Batey, A. N. Thadani, D. V. Smil, *Org. Lett.* **1999**, *1*, 1683; d) M. Ueda, N. Miyaura, *J. Org. Chem.* **2000**, *65*, 4450; e) C.-J. Li, Y. Meng, *J. Am. Chem. Soc.* **2000**, *122*, 9538; f) A. Fürstner, H. Krause, *Adv. Synth. Catal.* **2001**, *4*, 343; g) T. Huang, Y. Meng, S. Venkatraman, D. Wang, C.-J. Li, *J. Am. Chem. Soc.* **2001**, *123*, 7451.

[8] P(*t*-Bu)$_3$ has proven to be highly suited in rhodium-catalyzed additions of boronic acids to aldehydes: see ref.[7d]

[9] a) L. J. Gooßen, J. Paetzold, *Adv. Synth. Catal.* **2004**, *346*, 1665; b) F.-X. Chen, A. Kina, T. Hayashi, *Org. Lett.* **2006**, *8*, 341.

[10] Review: N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.

[11] T. Hayashi, M. Takahashi, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **2002**, *124*, 5052.

[12] a) F. Kakiuchi, S. Kan, K. Igi, N. Chatani, S. Murai, *J. Am. Chem. Soc.* **2003**, *125*, 1698; b) F. Kakiuchi, M. Usui, S. Ueno, N. Chatani, S. Murai, *J. Am. Chem. Soc.* **2004**, *126*, 2706.

[13] For the formation of alkoxo-rhodium species, see: a) S. E. Kegley, C. J. Schaverein, J. H. Freudenberger, R. G. Bergman, *J. Am. Chem. Soc.* **1987**, *109*, 6563; b) J. P. Collman, R. Boulatov, *Inorg. Chem.* **2001**, *40*, 560; c) S. Nückel, P. Burger, *Organometallics* **2001**, *20*, 4345.

[14] Hartwig et al. reported that the reaction between isolated aryl-rhodium(I) complexes and aldehydes resulted in the formation of ketone upon heating at 80 °C *via* the intermediate formation of a rhodium-alkoxide complexes, see: a) C. Krug, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 1674; b) C. Krug, J. F. Hartwig, *Organometallics* **2004**, *23*, 4594.