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Aryl Ketone Synthesis via Tandem Orthoplatinated Triarylphosphite-Catalyzed Addition Reactions of Arylboronic Acids with Aldehydes Followed by Oxidation

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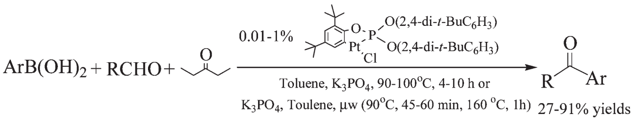

Tandem orthoplatinated triaryl phosphite-catalyzed addition reactions of arylboronic acids with aldehydes followed by oxidation to yield aryl ketones is described. 3-Pentanone was identified as a suitable oxidant for the tandem aryl ketone formation reaction. By using microwave energy, aryl ketones were obtained in high yields with the catalyst loading as low as 0.01%.

Transition-metal-catalyzed addition reactions of organoboron reagents with aldehydes have emerged as useful tools in organic synthesis.[1−8] Several transition-metal catalysts including Rh(I)/(II),[1,2] Pd(II),[3] Ni(0),[4] Cu(II),[5] and Fe(III)[6] complexes and, more recently, Ru(II) complexes[7] have been reported to catalyze this type of addition reactions. In our laboratory, we're interested in employing readily available anionic four-electron donor-based (type I) metalacycles,[9] a large family of cyclic organometallic compounds, as catalysts for such addition reactions.[10,11] In this context, we have recently documented type I palladacycle-catalyzed addition reactions of arylboronic acids with carbonyl-containing compounds.[10b,c] We have also employed type I platinacycle **1** as the catalyst for the addition reactions of arylboronic acids with aldehydes.[10a] To further the use of these readily

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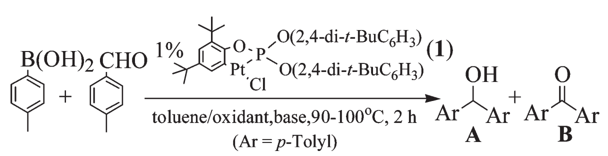
TABLE 1. Tandem Platinacycle 1-Catalyzed Reaction of *p*-Tolualdehyde with *p*-Tolylboronic Acid Followed by Oxidation [a]



entry	oxidant (mL)	base (equiv)	conv[b] (%)	A/B[b]
1	none	K_3PO_4 (3)	100	100/0
2	air	K_3PO_4 (3)	100	97/3
3	acetone (0.2)	K_3PO_4 (3)	100	51/49 [c]
4	2-butanone (0.2)	K_3PO_4 (3)	100	80/20 [d]
5	3-pentanone (0.2)	K_3PO_4 (3)	100	50/50
6	3-pentanone (0.2)	K_2CO_3 (3)	86	42/58
7	3-pentanone (0.2)	Cs_2CO_3 (3)	15	0/100
8	3-pentanone (0.2)	K_3PO_4 (2)	78	95/5
9	3-pentanone (0.2)	K_3PO_4 (1)	67	97/3
10	3-pentanone (0.2)	K_3PO_4 (0)	0	
11	3-pentanone (0.2)	K_3PO_4 (3)	100	65/35[e]
12	3-pentanone (0.2)	K_3PO_4 (3)	100	15/85[f]

[a] Reaction conditions: aldehyde (1.0 eqiuv), *p*-tolylboronic acid (2.0 equiv), toluene and oxidant (1 mL), base, 90−100 °C. [b] Ratio based on GC-MS. [c] 43% of aldol condensation product from aldehyde with acetone was observed. [d] 13% of aldol condensation product from aldehyde with acetone was observed. [e] Reaction temperature: 80 °C. [f] Reaction time: 7 h.

available, air-stable type I metalacycles as addition catalysts for organic synthesis, we became interested in combining type I metalacycle-catalyzed addition reactions with other bond-forming reactions in a sequential or tandem fashion. In particular, we're interested in combining such addition reactions with the secondary alcohol oxidation process to access aryl ketones.[12,13] Two groups have recently studied such additions followed by an oxidation reaction sequence.[14,15] Genet and Darses reported the preparation of diaryl ketones from Rh(I)-catalyzed addition of aldehydes with potassium trifluoro(organo)borates[14a,b] or arylboronic acids[14c] followed by an oxidation reaction. Wu reported a one-pot synthesis of diaryl ketones via palladium-catalyzed reaction with arylboronic acids with aldehydes, in which 2 equiv of aldehydes was required.[15] While these protocols are useful for diaryl ketone synthesis, there are drawbacks associated with them, e.g., high catalyst loading, requirement of 2 equiv of aldehydes, and/or limited substrate scope. Based on the consideration that low catalyst loading such as 0.05% have been achieved for type I platinacycle-catalyzed addition reaction of arylboronic acids with aldehydes,[10a] we reasoned that if a suitable oxidant for the oxidation step could be identified, a highly efficient ketone synthesis protocol could be developed. Herein, we report our results on such tandem type I platinacycle-catalyzed addition of arylboronic acids with aldehydes followed by oxidation for the synthesis of aryl ketones. In addition, we also report a microwave-assisted aryl ketone synthesis with shortened reaction time and low catalyst loading.

We began our study with the identification of a suitable oxidant for the oxidation step for type I platinacycle **1**-catalyzed tandem reaction with *p*-tolualdehyde as the substrate and *p*-tolylboronic acid as the nucleophile. Our results are summarized in Table 1. We first used air as the oxidant for the oxidation step. We found that although the addition reaction proceeded smoothly to yield the alcohol under air at 90−100 °C in 2 h, the oxidation of the alcohol to ketone was very sluggish and only 3% of ketone was observed (Table 1, entries 1 and 2). As acetone has been well-established as an oxidant for secondary alcohol oxidation,[14a,b] we seek to use it as the oxidant. We found indeed more ketone product (49%) was formed, which was promising (Table 1, entry 3). However, one drawback of using acetone as the oxidant was that the aldol condensation between *p*-tolualdehyde and acetone under the reaction conditions occurred significantly. Because the aldol condensation is known to be sensitive to steric hindrance, we reasoned that increasing the steric hindrance of the ketone oxidants might overcome this side reaction issue. We thus tested 2-butanone and 3-pentanone as the oxidants. We found although the aldol condensation can still be observed for 2-butanone (Table 1, entry 4), 3-pentanone was an excellent oxidant, with almost no aldol condensation between aldehyde and 3-pentanone being observed (Table 1, entry 5). By using 3-pentanone as the oxidant, we then tested other bases for the reaction, and found K_3PO_4 was the most effective base (Table 1, entries 5−7). Higher yields were observed for the ketone formation with the use of larger amounts of K_3PO_4, and the best results were obtained by using 3 equiv of K_3PO_4 (Table 1, entries 5 and 8−10). We further found that the oxidation step was influenced by the reaction temperature and time. Lowering the temperature from 90 to 80 °C led to a decreasing yield of ketone (Table 1, entry 11). Lengthening the reaction time led to more ketone formation (Table 1, entry 12).

With 3-pentanone as the oxidant and K_3PO_4 as the base, we tested other aldehydes and arylboronic acids for this platinacycle **1**-catalyzed tandem ketone formation, and our results are listed in Table 2. As shown in Table 2, good yields were obtained for aromatic aldehydes bearing electron-donating or electron-withdrawing substituents (Table 2, entry 1−17). Impressively, we found that aliphatic aldehydes were suitable substrates for the tandem reactions, and alkyl aryl ketones were obtained in good yields (Table 2, entry 18−21). It should be mentioned that, to our knowledge, these represent the first examples of direct access to aryl alkyl ketones from alkyl aldehydes with arylboronic acids via the tandem addition−oxidation reaction. We also found phenylboronic acids bearing a CH_3 or CH_3O group were better reagents than F-containing phenylboronic acid as a lower yield was observed with 4-fluorophenylboronic acid as the reagent (Table 2, entry 22). Since platinacycle **1** could catalyze the addition reaction of arylboronic acids with aldehydes with the catalyst loading of 0.05%,[10a] we also tested the tandem reaction at lower catalyst loadings. We found that reducing the catalyst loading influenced the oxidation step. By extending the reaction time to 18 h, the catalyst loading could be reduced to 0.2% with good isolated yield (Table 2, entry 23). Further lowering the catalyst loading led to a very slow formation of ketone (Table 2, entry 24).

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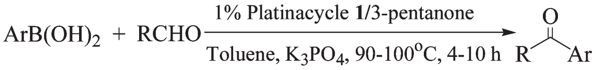
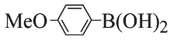
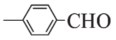
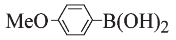
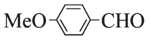
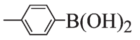
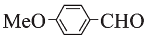
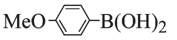
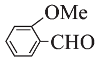
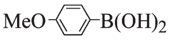
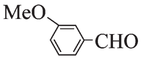
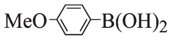
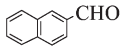
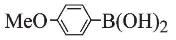
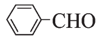
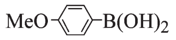
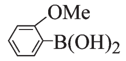
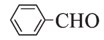
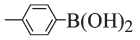
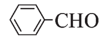
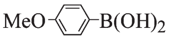
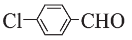
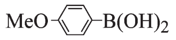
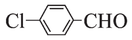
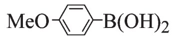
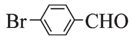
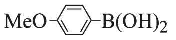
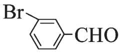
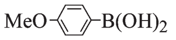
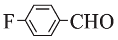
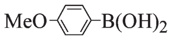
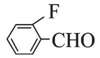
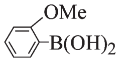
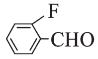
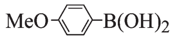
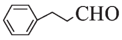
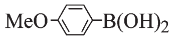
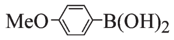
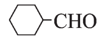
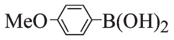
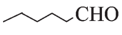
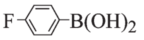
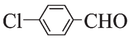
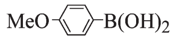
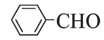
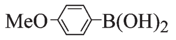
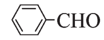
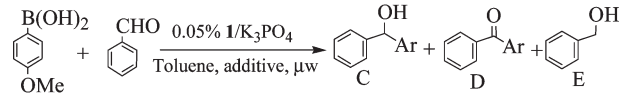
TABLE 2. Orthoplatinated Triaryl Phosphite 1-Catalyzed Formation of Diaryl Ketones from Aldehydes and Arylboronic Acids[a]



Entry	Ar'-B(OH)$_2$	RCHO	Yield(%)[b]
1			87
2			82
3			75
4			86
5			81
6			83
7			88
8			84[c]
9			80
10			81
11			91
12			87[c]
13			87
14			82
15			84
16			81
17			70[d]
18			82
19			71
20			76
21			75
22			27[e]
23			78[f]
24			51[g]

[a]Reaction conditions: aldehydes (1.0 equiv), arylboronic acid (2.0 equiv), 1% platinacycle **1**, 3-pentanone/toluene (1:4, 1 mL), K_3PO_4 (3.0 equiv), 90−100 °C. [b]Isolated yields. [c]1.5 equiv of $ArB(OH)_2$ was used. [d]88% conversion was observed for the oxidation step. [e]The aldol condensation product of acetone with *p*-chlorobenzaldehyde was the major product. [f]Catalyst loading: 0.2%. Reaction time: 18 h. [g]Catalyst loading: 0.1%. Reaction time: 24 h. 49% of (*p*-methoxyphenyl)-phenylmethanol was observed.

TABLE 3. Microwave-Assisted, Platinacycle 1-Catalyzed Addition Reactions of Arylboronic Acids with Aldehydes [a]



entry	T (°C), time (min.)	additive	conv[b] (%)	ratio of C/D/E[c]
1	90, 30		96	96:4:0
2	100, 30		97	94:5:1
3	120, 30		97	85:9:6
4	140, 30		99	74:16:10
5	90, 60	acetone	99	69:27:0[d]
6	160, 60	acetone	99	24:65:0[e]
7	90, 30; 160, 30	acetone	100	11:84:0[f]
8	90, 30; 160, 30	2-butanone	100	10:86:0[g]
9	90, 30; 160, 30	3-pentanone	100	14:85:0[h]

[a]Reaction conditions: aldehydes (1.0 equiv), arylboronic acids (2.0 equiv), **4** (0.05%), toluene (1 mL), K_3PO_4 (3.0 equiv), microwave (100 °C, 45 min, 160 °C, 45 min). [b]Based on ^{1}HNMR. [c]Based on GC−MS analysis. [d]4% of 4-phenyl-3-buten-2-one was oberved. [e]10% of 4-phenyl-3-buten-2-one was oberved. [f]5% of 4-phenyl-3-buten-2-one was oberved. [g]4% of 1-phenyl-1-penten-3-one was oberved. [h]1% of 2-methyl-1-phenyl-1-penten-3-one was oberved.

To further decrease the catalyst loading, we turned our attention to use microwave energy for the tandem reaction as temperatures for reactions under microwave irradiation could be much higher than that of reactions being heated by conventional methods such as heating in oil bath.[16,17] We surmised that due to the temperature difference between microwave-assisted reactions and reactions being heated by conventional methods, carrying out such tandem addition−oxidation reactions under microwave irradiation might need lower catalyst loading and require shorter reaction time compared to the same reaction being heated under conventional heating methods. We first tested microwave-assisted platinacycle **1**-catalyzed reaction of benzaldehyde with *p*-methoxyphenylboronic acid with 0.05% catalyst loading. We found without additionally added oxidants such as acetone, benzaldehyde served as the oxidant for the ketone formation and low yields of the ketone product were observed (Table 3, entries 1−4). Significantly, the addition reactions were observed to be completed in 30 min, which was much shorter than the time required for this addition reaction being heated under oil-bath heating.[10a] We next tested the use of acetone as the oxidant for the reaction. We found while the addition reaction occurred smoothly at 90 °C, only 27% of ketone was observed (Table 3, entry 5), suggesting that a higher reaction temperature and/or longer reaction time would be needed to achieve higher yields of ketones. We thus tested the reaction at 160 °C. We found that although the amount of the ketone was increased, 10% of the aldol condensation product of acetone with aldehyde was observed (Table 3, entry 6). We next conducted the tandem reaction with ramped temperatures: 90 °C for 30 min for the addition reaction and 160 °C for 45 min for the oxidation reaction. We found less aldol condensation byproduct was formed (Table 3, entry 7). We also tested the use of 2-butanone and 3-pentanone as oxidants with such a gradient temperature setting and found 3-pentanone gave the best result (Table 3, entries 7−9).

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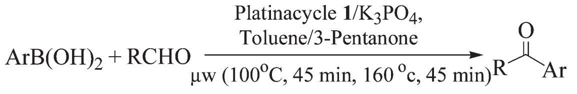
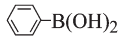
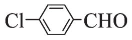
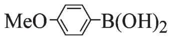
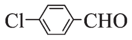
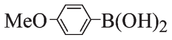
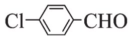
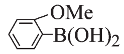
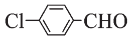
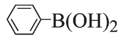
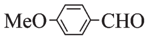
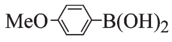
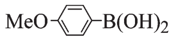
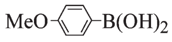
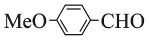
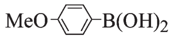
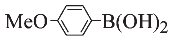
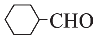
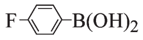
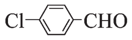
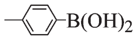
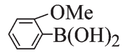
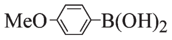
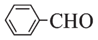
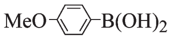
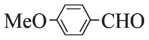
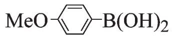
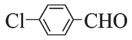
(16) (a) Kappe, C. O.; Dallinger, D.; Murphree, S. S. *Practical Microwave Synthesis for Organic Chemists: Strategies, Instruments and Protocols*; Wiley-VCH: Weinheim, 2009. (b) Larhed, M., Olofsson, K., Eds. *Microwave Methods in Organic Synthesis*. Springer: Berlin, 2006. (c) *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006. (d) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, 2005. (e) Lidstrom, P., Tierney, J. P., Eds. *Microwave-Assisted Organic Synthesis*; Blackwell Publishing: Oxford, 2005.

(17) (a) Polshettiwar, V.; Varma, R. S. *Acc. Chem. Res.* **2008**, *41*, 629–639. (b) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563–2591. (c) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653–661.

TABLE 4. Microwave-Assisted, Platinacycle 1-Catalyzed Reactions of Arylboronic Acids with Aldehydes for Ketone Synthesis [a]



Entry	Ar'-B(OH)$_2$	RCHO	Catalyst Loading	Yield(%)[b]
1			0.05	76
2			0.05	89
3			0.05	85 [c]
4			0.05	82
5			0.05	83
6			0.05	87
7			0.05	85 [c,d]
8			0.05	85
9			0.05	84
10			0.05	77
11			0.1	38 [e]
12			0.03	83 [f]
13			0.03	86 [f]
14			0.01	85 [f]
15			0.01	81 [f]
16			0.01	88 [f]

[a] Reaction conditions: aldehydes (1.0 equiv), arylboronic acids (2.0 equiv), **1** (0.01−0.05%), toluene/3-pentanone (4/1,1 mL), K_3PO_4 (1.0 equiv), microwave (100 °C, 45 min; 160 °C, 45 min). [b] Isolated yields. [c] 1.5 equiv of ArB(OH)$_2$ was used. [d] 7% of aldol condensation product of 3-pentanone with benzaldehyde was observed. [e] 50% of aldol condensation product of 3-pentanone with *p*-chlorobenzaldehyde was observed. [f] Microwave (100 °C, 60 min; 160 °C, 60 min).

With 0.05% catalyst loading of platinacycle **1** and 3-pentanone as the oxidant, we examined other arylboronic acids and aldehydes. Good to high yields were observed for all arylboronic acids/aldehydes tested (Table 4, entries 1−10) except for 4-fluorophenylboronic acid (Table 4, entry 11). We further attempted to lower the catalyst loading and found with even 0.01% catalyst loading the tandem reaction still occurred efficiently (Table 4, entries 9−13). Compared to the reported ketone preparation via tandem Rh(I)- and Pd(II)-catalyzed addition reactions followed by oxidation,[14,15] which required high catalyst loading, limited substrate scope, and/or extra equivalent of aldehydes, our platinacycle **1**-catalyzed tandem addition−oxidation protocols for the synthesis of aryl ketones competes favorably with these reported methods.

In summary, we have demonstrated that type I platinacycle **1**-catalyzed addition reactions of arylboronic acids with aldehydes can be combined with the oxidation of alcohol process in tandem fashion to access aryl ketones. 3-Pentanone was identified as a suitable oxidant for the oxidation of alcohol step. By using microwave energy, platinacycle **1**-catalyzed addition followed by oxidation could be realized with low catalyst loading, as low as 0.01%. Our study provides an efficient method to synthesize aryl ketones. Our future work will be directed to explore other tandem/sequential reactions involving the addition reaction of arylboronic acids with aldehydes as part of the reaction sequence.

Experimental Section

Typical Procedure for Platinacycle 1-Catalyzed Reactions of Arylboronic Acids with Aldehydes for Ketone Synthesis. To a vial containing 2-methoxybenzaldehyde (0.25 mmol), 4-methoxyphenylboronic acid (0.50 mmol), K_3PO_4 (0.75 mmol), and **1** (1 mol %) were added toluene (0.80 mL) and 3-pentanone (0.20 mL). After the mixture was stirred at 90−100 °C for 4−10 h, the reaction was extracted by CH_2Cl_2. Column chromatography on silica gel with ethyl acetate/hexane (v/v = 1:10) afforded the ketone product 2-methoxyphenyl 4-methoxyphenyl ketone: ^{1}H NMR (CDCl$_3$, 600 MHz) δ 7.81 (d, J = 7.2 Hz, 2H), 7.44 (t, J = 7.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.03 (t, J = 7.2 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H), 3.86 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (CDCl$_3$, 150 MHz) δ 195.0, 163.5, 157.0, 132.3, 131.4, 130.7, 129.3, 129.2, 120.4, 113.4, 111.3, 55.6, 55.4.

Typical Procedure for Microwave-Assisted Platinacycle 1-Catalyzed Reactions of Arylboronic Acids with Aldehydes for Ketone Synthesis. To a 10-mL pressure vial containing 4-methoxybenzaldehyde (0.50 mmol), 4-methoxyphenylboronic acid (1.0 mmol), K_3PO_4 (0.50 mmol), and platinacycle **1** (0.05 mol %) were added toluene (1.6 mL) and 3-pentanone (0.4 mL). After the mixture was irradiated by microwave at 100 °C for 45 min and then irradiated at 160 °C for another 45 min, the reaction was quenched by adding a small amount of water. Extraction with CH_2Cl_2 and column chromatography on silica gel with ethyl acetate/hexane (v/v = 1:10) afforded the product, bis(4-methoxyphenyl) ketone: ^{1}H NMR (CDCl$_3$, 600 MHz) δ 7.78 (4H, d, J = 7.2 Hz), 6.96 (4H, d, J = 7.2 Hz), 3.88 (3H, s); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 194.4, 162.8, 132.2, 130.7, 113.4, 55.4.

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Supporting Information Available: General procedures and characterizations of tandem platinacycle-catalyzed addition followed by oxidation reactions. This material is available free of charge via the Internet at http://pubs.acs.org.