# DEVELOPMENT OF HIGHLY EFFICIENT TRANSITION METAL-CATALYZED ADDITION REACTIONS

by

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# Abstract

DEVELOPMENT OF HIGHLY EFFICIENT TRANSITION METAL-CATALYZED ADDITION REACTIONS

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Development of new and efficient reactions as powerful tools for synthetic chemistry is one of the most important tasks in modern chemistry. Transition metal-catalyzed carbon-carbon bond-forming reactions including addition reactions are some of the most powerful transformations in organic synthesis. My research is on developing highly efficient transition metal-catalyzed addition reactions as powerful tools for organic synthesis.

There are two parts of my Ph. D. dissertation research projects. In the first part, based on our understanding on transmetalation and reductive elimination of palladium catalysis, we minimized the decomposition of catalysts and developed a series of new, highly efficient Pt(II), Pd(II), Rh(I) and Cu(II)-catalyzed addition reactions of organoboron reagents with carbonyl-containing compounds. Since Pt complexes can undergo reductive elimination very reluctantly, we explored the platinacycle-catalyzed addition reaction of arylboronic acids with aldehydes with low catalyst loadings. However, the low catalyst loading catalysis with platinacycles as catalysts was achieved at the expense of the catalyst catalytic activity. In order to minimize the decomposition of catalyst as well as keep the catalytic activity, a new anhydrous condition of addition

reactions was established and a novel non-transmetalation mechanism of the Pd-catalyzed addition reaction was proposed and demonstrated. Under the guidance of the new reaction mechanism, we pinpointed that some addition reactions which are thought to be hardly achievable before may be accomplished now. By using the anhydrous condition, we explored Cu-catalyzed addition reactions of arylboroxines with carbonyl-containing compounds and Rh-catalyzed addition reactions of arylboroxines with ketones.

In the second part, to make the addition reactions we developed in the first part be more powerful, we explored new tandem/sequential reactions involved such addition reactions as one of bond-forming reactions. Specifically, we combined Pt(II)-catalyzed 1,2-addition reactions of arylboronic acids and aldehydes with the secondary alcohol oxidation process in a tandem fashion to synthesis aryl ketones from readily available aldehydes and arylboronic acids. We also developed the synthesis of β-arylated ketones via the aldol condensation of aldehydes with methyl ketones followed by transition metal-catalyzed addition reaction in a sequential and tandem fashion. Such sequential/tandem protocols offer us rapid entry to synthesize complex materials or biological active compounds from simple precursors.

*This Dissertation is Dedicated*

*To My Grandparents: Liao, Qinsheng and Li, Juanxia*

*(廖勤生 与 李娟霞)*

*To My Parents: Liao, Yiwen and Xie, Minyan*

*(廖宜文 与 谢敏颜)*

*And To My Wife: Huang, Liang*

*(黄亮)*

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# Introduction

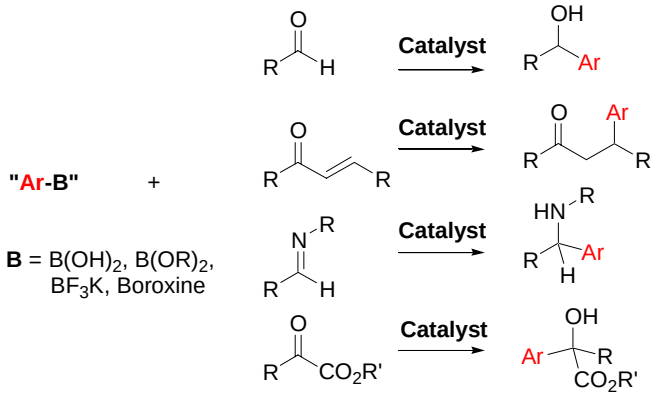
Transition metal-catalyzed carbon-carbon bond-forming reactions including addition reactions are some of the most powerful transformations in organic synthesis. They have been extensively employed in the synthesis of a wide variety of organic compounds ranging from bioactive compounds, pharmaceuticals to other materials.

In these transition metal-catalyzed addition reactions, organometallic reagents such as magnesium,[1] tin,[2] zinc,[1c,3] silicon[2b,4] and titanium[5] reagents have been widely employed as nucleophiles because of their high reactivity, stereospecificity and regioselectivity. However, these organometallic reagents are air/moisture-sensitive, high toxic and/or have a poor functional group compatibility. Transition metal-catalyzed addition reactions of organoboron reagents with carbonyl-containing compounds and analogs have recently emerged as very useful transformation in organic synthesis because organoboron reagents are nontoxic, air/moisture-stable and functional group compatible.[6,7,8,9,10,11,12,13,14] So far to the year of 2007 when I started my dissertation projects research, Rh(I), Pd(II), Ni(0) and Cu(II) catalysts have been reported to catalyze addition reactions of organoboron reagents with aldehydes, α,β-unsaturated ketones, α-ketoesters, and aldimines, giving as Scheme I-1.

Rh(I)-catalyzed addition reactions, no matter 1,2-addition to the aldehydes or 1,4-addition to the α,β-unsaturated ketones, have been greatly developed even in the field of asymmetric catalysis. In 1998, Hayashi and Miyaura reported the first example of rhodium-catalyzed asymmetric 1,4-addition reactions.[14b] The reaction conditions described above have been frequently used as the standard conditions for

rhodium-catalyzed asymmetric reactions. Several years later, Hayashi and his co-workers described the development of an asymmetric 1,4-addition reaction of arylboronic acids to 3-substituted maleimides, furnishing 3,3-disubstituted succinimides in a high regio- and enantioselectivity.[14c] In 1998, Miyaura and co-workers reported the enantioselective Rh-catalyzed 1,2-addition of phenylboronic acid to naphthaldehyde by using the (*S*)-MeO-MOP ligand giving naphthylphenylmethanol in 78% yield and 41% ee.[10w] In 2006, Zhou reported an effective protocol for asymmetric addition of arylboronic acids to aldehydes by using Rh(I)/chiral spiromonophosphite to provide diarylmethanols in excellent yields with up to 87% ee.[10h] That result is so far the highest enantioselective one for Rh-catalyzed addition of arylboron reagents to aldehydes.

**Scheme I-1** Transition Metal-Catalyzed Addition Reactions of Arylborons




**Catalyst** : Rh(I)/Rh(II), Pd(II), Pt(II), Ni(0), Ru(II), Co(II), Cu(II), Fe(III)

As for Pd(II)-catalyzed addition reactions, palladium-catalyzed addition reaction of arylborons was first reported in 1995 by Uemura, who demonstrated that palladium(0)/$SbCl_3$ catalyzed the conjugate addition to α,β-unsaturated carbonyl compounds. Minnaard reported the first enantioselective palladium-catalyzed conjugate addition of arylboronic acids to a variety of α,β-unsaturated compounds in 2006.[13a] In the

year of 2005, Ohta documented the first example of Pd(II)-catalyzed 1,2-addition reaction that palladium(0) complexes coordinated by phosphine ligands catalytically induced the 1,2-addition reaction of arylboronic acids to aldehydes in the presence of base and a catalytic amount of chloroform.[7e] Soon after, our group reported anionic four-electron donor-based palladacycle-catalyzed 1,4-additions of arylboronic acids with α,β-unsaturated ketones and 1,2-additions of arylboronic acids with aldehydes and β-ketoesters in which catalysts were widely employed for cross-coupling reactions.[8] There is still one attractive example for an intramolecular addition reaction of arylboronic acids to ketone catalyzed by cationic palladium complex catalyst which reported by Lu.[7f]

There were three examples on Ni-catalyzed addition reactions.[6] In 2005，Shirakawa reported Ni-catalyzed addition reaction of arylboronates with aldehydes in the present of 4-octyne as ligand.[1b] Later, Kondo and Aoyama developed Ni-catalyzed addition reaction of arylboroxines with aldehydes using phosphine as ligand which made the extension for an asymmetric version of Ni-catalyzed arylation possible.[1a] Nearly at the same time as Shirakawa' work, Yorimitsu and Oshima reported the first example of a transition metal-catalyzed 1,2-addition reaction of alkylboranes with aldehydes with $Ni(cod)_2$/*t*-$Bu_3P$.[1c] There are only two reports by Shibasaki and Kanai on addition reactions of alkenyl and arylboronates to aldehydes and ketones catalyzed chiral CuF complex.[10t,10x]

During the years from 2007 to 2011 while I was preparing my dissertation, some significant improvements on addition reactions have been achieved by our group and other research groups. Our group reported $[Rh(COD)Cl]_2$ and $Ni(COD)_2$/4-$RCOC_6H_4Cl$-catalyzed addition reactions of arylborons with aldehydes.[15] In the year of 2009,

Yamamoto and Miyaura reported Ru(II)/bidentate chiral phosphoramidite complexes-catalyzed asymmetric addition reactions of arylboronic acids with aldehydes to achieve excellent enantioselectivities which was the first example for Ru(II)-catalyzed 1,2-addition reactions of arylborons with aldehydes.[16] Soon later in 2010, Cheng reported that cobalt was successfully employed to catalyze 1,2-addition reactions of arylboronic acids with aldehydes which realized less expensive transition-metal catalyzed 1,2-addition reaction of arylborons with reasonable scope of aldehydes and an asymmetric version.[17] Xu and Lin developed a novel chiral $C_2$-symmetric tetrahydropentalenes ligands for highly enantioselective Rh-catalyzed addition reaction of arylboronic acids with *N*-tosylarylimines and nitroalkenes.[18] In 2009, less expensive transition metals such as iron and copper have also been catalyzed 1,2-addition reaction of arylboronic acids with electron-deficient aryl aldehydes.[19] In 2010, Ni(II)/*N*-heterocarbene-catalyzed 1,2-addition reactions of arylboronates with unactivated ketones and aldehydes have been reported, which are the first examples of transition metal-catalyzed 1,2-addition reactions of organoborons with regular ketones.[20]

Based on the review on the development of transition metal-catalyzed addition reactions, we found that a number of ligands and transition metal catalysts have been well developed for addition reactions. However, many challenges in this field remain.

First, the high catalyst loading, typically 3% or more, is necessary since the reductive elimination of catalysts, which occurs after the transmetalation steps, would cause significant decomposition of catalyst. Can we reduce these expensive transition catalysts to a significantly lower level?

Second, most of reported addition reactions were catalyzed by expensive or rare

transition metals like rhodium, palladium and ruthenium. Can we develop some highly efficient, environmentally friendly and less expensive catalysts for these addition reactions?

Third, some substrates such as ketones and alkylboronic acids are rarely successfully employed in 1,2-addition reactions. The 1,2-addition reactions of much less reactive ketones has been largely limited to activated substrates and intramolecular reactions or must be preceded by boron-to-zinc transmetalation. The 1,2-addition of alkylboronic acids has not been reported since alkyl-boron bonding is less reactive to be transmetalated and the following β-hydride elimination easily takes place even the transmetalation of alkyls occurred. Therefore, development of addition reactions of these less reactive substrates is one of major challenges in this field.

Lastly, sequential/tandem reaction could form several bonds in one sequence without isolating the reaction intermediates, it offers the possibility of rapid entry to complex building blocks from relatively simple precursors. The development of new tandem/sequential reactions represents one of the most active frontiers in synthetic chemistry. Therefore, can these attractive addition reactions be combined with other carbon-carbon-bonding formations into a sequential/tandem fashion to make it more powerful?

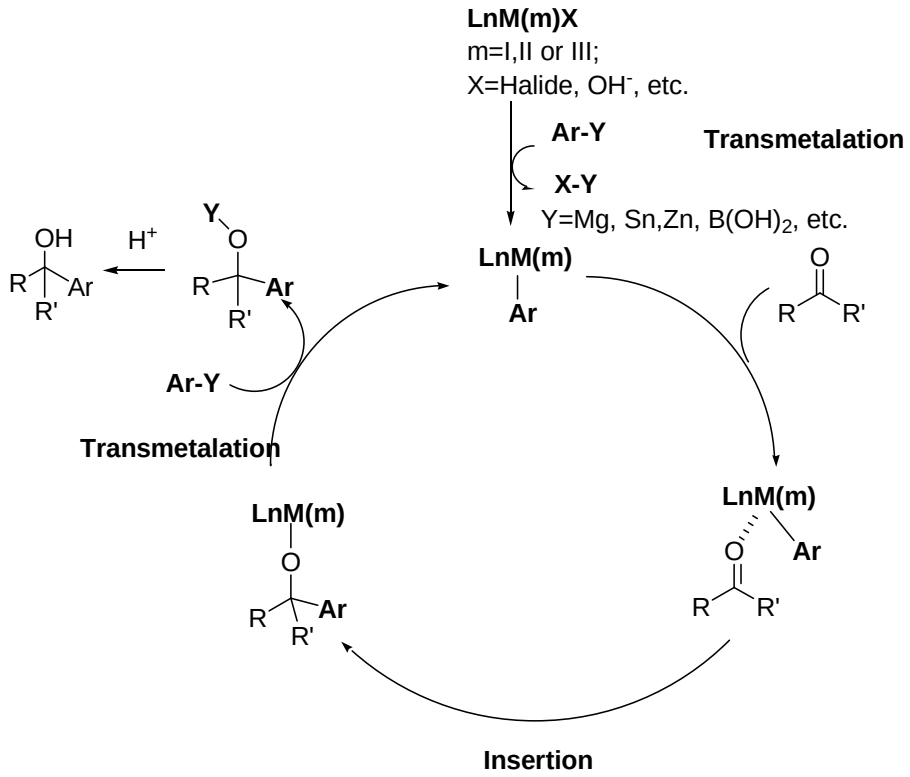
It is of our primary concern to develop highly efficient transition metal-catalyzed addition reactions with organoborons, especially focusing on addressing the challenges mentioned above in the addition reaction field.

Extensive study established that there are three key steps in the catalytic cycles of transition metal-catalyzed addition reactions: transmetalation of an organometallic

reagent to form an organometallic complex; coordination of carbonyl-containing compounds with organometallic complex; insertion of aryl or alkyl group from organometallic complex to carbonyl-containing compounds; and another transmetalation of organometallic reagents to form the addition product and regenerate the organometallic complex (Figure I-1).

The reductive elimination may happen after the first transmetalation step and generate zero valent transition metal complexes or metal particles which cannot catalyze addition

**Figure I-1.** Mechanism of Transition Metal-Catalyzed Addition Reaction




reactions. Therefore, we reasoned that minimizing the reductive elimination of diorganometallic complex would be the key to develop highly efficient catalysis with low catalyst loadings. Two strategies were considered. The first strategy was to use highly efficient catalysts for addition reactions, for which the catalysts undergo slow reductive

elimination. Another strategy was to avoid the reductive elimination, which may be more challenge: to explore a new catalysis pathway that the addition reaction might take place without the occurrence of transmetalation. Achieving such addition reactions (aryl transferring) without transmetalation could prevent catalysts from decomposition and thus may offer us new catalysis opportunities such as low catalyst loading catalysis, expanded substrates/nucleophile scope and new bond-forming reactions.

Based on our understanding on mechanisms of addition reactions, my dissertation started from exploring the reductive elimination reluctant catalysts for addition reactions where we found that diorganoplatinate complex was a good choice. Although diorganoplatinate complex can be reluctant to undergo reductive elimination even at elevated temperature and is excellently efficient catalyst for addition reaction, the necessary harsh reaction condition to complement its relative low catalytic capability spurred us to develop a new highly efficient catalysis system for addition reaction under mild reaction conditions. We hypothesized a new reaction pathway for Type I palladacycle-catalyzed addition reactions: the addition reactions (aryl transferring) might take place to afford addition product without the occurrence of transmetalation**.** We established such possibility and further demonstrated this novel mechanism. Relied on this mechanism, we minimized the decomposition of catalysts and therefore developed some new and efficient transition metal-catalyzed addition reactions which have never been achieved under the tutoring of reported mechanism. These reactions include Cu(I)/bipyridine-catalyzed addition reactions of arylboroxines with carbonyl-containing compounds and Rh(I)-catalyzed addition reaction of organoborons with ketones. These developments of addition reaction principles and methodologies constitute the first major

part of this dissertation.

Relied on our understanding of the addition reaction mechanism, we believed that any elementary steps in catalytic cycles might be controlled. Such controls, especially combined with other bond-forming processes into a sequential/tandem fashion, could provide us unprecedented opportunities to develop new reactions, thus making these transition metal-catalyzed addition reactions be more powerful for organic synthesis. A sequential/tandem reaction could form several bonds in one sequence without isolating the intermediates and/or changing the reaction conditions. It obviously would be much more efficient compared to the stepwise formation of individual bonds in the target molecules by conventional procedures. Sequential/tandem reactions would minimize the waste and prepurification labor compared to stepwise reactions. For such advantages of sequential/tandem reactions, one of the major works in my dissertation is combining the addition reaction with other bond-forming reactions such as the aldol condensation or oxidation reaction into one sequence to make these reactions be more powerful for organic synthesis. Development of these new tandem/sequential reactions constitutes the second major part of this dissertation.

# Part I. Developments of Addition Reaction Principles and Methodologies

## Chapter 1. Platinum-Catalyzed 1,2-Addition Reactions of Arylboronic Acids with Aldehydes: Low Catalyst Loading Catalysis

### 1.1 Introduction

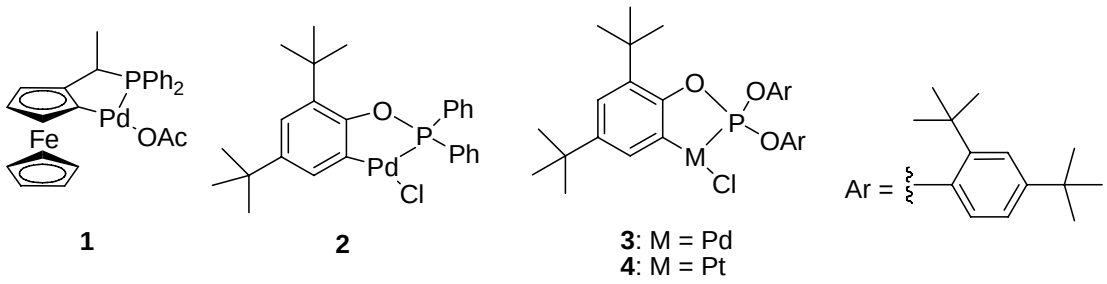
Transition metal-catalyzed addition reactions of organoboronic acids with carbonyl-containing compounds and analogs have recently emerged as a very useful transformation in organic synthesis because organoboronic acids are nontoxic, air/moisture-stable and practically useful.[6-14] Rh(I), Pd(II), Ni and Cu catalysts have been reported to catalyze addition reactions of arylboronic acids with aldehydes, α,β-unsaturated ketones, α-ketoesters, and aldimines.

Over the past years, while a number of ligands and transition metal catalysts have been developed, challenges in this field remain. For examples, can the high catalyst loading, typically 3% or more, be reduced a significantly lower level? In this chapter, we describe our effort in realizing such possibilities, specifically, the investigation of the addition reactions of arylboronic acids with aldehydes in the presence of an orthoplatinated triarylphosphite catalyst, with the catalyst loading of as low as 0.01%.

In our group's previous work, we reported palladacycles **1-3** as highly efficient catalysts for the addition reactions of arylboronic acids with carbonyl-containing compounds, with palladacycle **3** exhibiting the highest catalytic activity.[8b] In that study, we observed that palladacycle **3**-catalyzed addition reaction of phenylboronic acid with 2-bromobenzaldehyde yielded a significant amount of cross-coupling reaction product

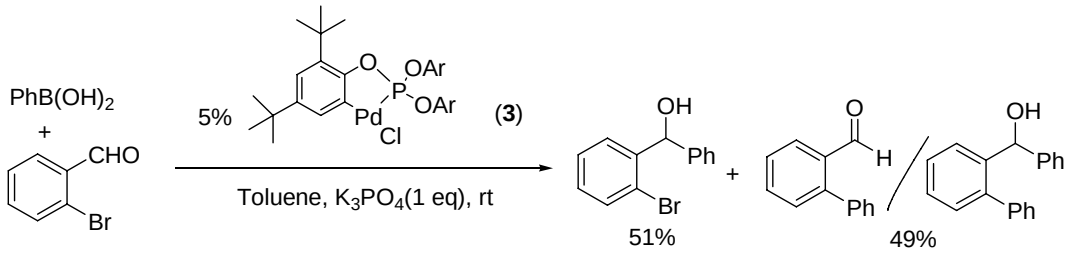
(Scheme 1.1). Such an observation suggested that the reductive elimination occurred during this palladacycle **3**-catalyzed addition reaction, a side reaction that should be responsible for the catalyst decomposition. Thus, minimizing or avoiding such reductive elimination might be the key to develop highly efficient catalysts with a low catalyst loading.

**Figure 1.1** Palladacycles **1-3** and Platinacycle **4**




**1** **2** **3**: M = Pd **4**: M = Pt

**Scheme 1.1** Palladacycle **3**-Catalyzed Addition Reaction of Phenylboronic Acid with 2-Bromobenzaldehyde

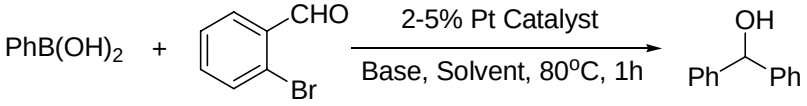


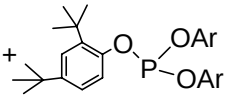

Recent studies also established that diorgano Pt were very reluctant to undergo reductive elimination,[5,6] suggesting that platinum complexes might be the transition metal catalysts to achieve low catalyst loading. As the third element in the nickel triad, Pt is softer than Ni and Pd. We envisioned that the soft nature of platinum and reluctance of reductive elimination of diorgano Pt complexes might render Pt complexes exhibiting interesting catalysis properties for such 1,2-addition reactions.

## 1.2 Catalysts and Reaction Condition Screening for Addition Reaction of Arylboronic Acids with Aldehydes

As diorgano Pt complexes have been demonstrated to undergo reductive elimination very reluctantly even at elevated temperature,[11-12] we reasoned that platinum complexes

**Table 1.1** Platinum-catalyzed Addition Reaction of Phenylboronic Acid with 2-Bromobenzaldehyde




| Entry | Pt Catalyst | Solvent | Blase | Conversion(%)[b,c] |
|---|---|---|---|---|
| 1 | $Pt(COD)Cl_2$ | Toluene | $K_3PO_4$ | <1 |
| 2 | $Pt(COD)Cl_2 + PPh_3$ | Toluene | $K_3PO_4$ | 5 |
| 3 | $Pt(COD)Cl_2 + PCy_3$ | Toluene | $K_3PO_4$ | 4 |
| 4 | $Pt(COD)Cl_2$ +  | Toluene | $K_3PO_4$ | <1 |
| 5 | **4** | Toluene | $K_3PO_4$ | 55[d] |
| 6 | **4** | Toluene | $K_3PO_4$ | 99 |
| 7 | **4** | Toluene | $K_3PO_4$ | 99.5[e] |
| 8 | **4** | Toluene | $K_3PO_4$ | 40[f] |
| 9 | **4** | Toluene | No base | 20 |
| 10 | **4** | THF | $K_3PO_4$ | 88 |
| 11 | **4** | Dioxane | $K_3PO_4$ | 81.5 |
| 12 | **4** | $CH_2Cl_2$ | $K_3PO_4$ | 89 |
| 13 | **4** | Toluene | $K_2CO_3$ | 98.5 |
| 14 | **4** | Toluene | KOH | 78 |
| 15 | **4** | Toluene | $Na_2CO_3$ | 20 |
| 16 | **4** | Toluene | $Cs_2CO_3$ | 57 |

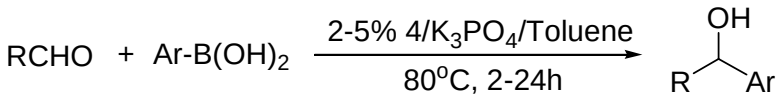
a. Reaction conditions: aldehydes (1.0 equiv), phenylboronic acid (2.0 equiv), toluene (2ml), $K_3PO_4$ (3 equiv) 60-80 $^oC$. b. Conversion based on $^1H$ NMR. c. cross-coupling product was observed in < 1%. d. Reaction was carried out at room temperature. e. $K_3PO_4$ (1 equiv). f. $K_3PO_4$ (0.5 equiv)

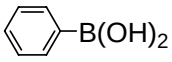
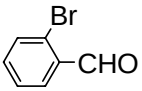
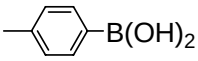
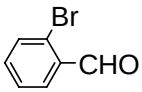
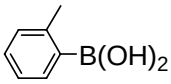
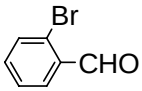
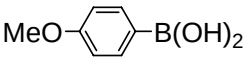
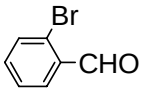
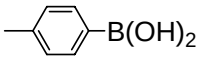
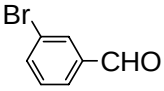
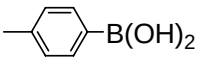
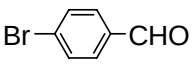
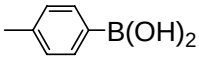
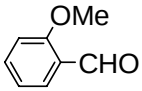
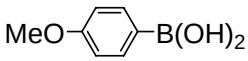
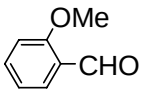
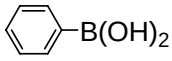
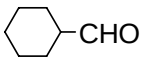
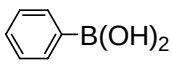
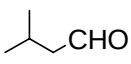
could catalyze such addition reaction with minimized reductive elimination side-reaction. Our study thus began with the addition reaction of phenylboronic acid with 2-bromobenzaldyhyde by testing several Pt complexes. We found although $[Pt(COD)_2Cl]_2$, $[Pt(COD)_2Cl]_2$ + $PPh_3$ and $[Pt(COD)_2Cl]_2$ + $PCy_3$ were ineffective catalyst systems (Table 1.1, entries 1-3), readily available platinacycle **4**[7] exhibited promising catalytic activity, especially at high temperature (Table 1.1, entries 5 and 6) with less than 1% cross-coupling product being observed. These results suggested that virtually no reductive elimination occurred at 80 $^oC$, consistent with previously reported cross-coupling studies.[11,21] Further study revealed that toluene was the best solvent and $K_3PO_4$ and $K_2CO_3$ were the best bases (Table 1.1, entries 5-16).

### 1.3 Platinacycle-Catalyzed Addition Reactions of Arylboronic Acids with Aldehydes

With toluene as solvent and $K_3PO_4$ as base, we employed platinacycle **4** as catalyst for the addition reaction of a number of aldehydes and arylboronic acids, and our results are listed in the Table 2. We found that platinacycle **4** was a general catalyst not only for the addition of arylboronic acids with aromatic aldehydes, including activated and deactivated ones (Table 2, entries 1-8), but also for the addition of arylboronic acid with aliphatic aldehydes (Table 2, entries 9-10). Steric hindrance didn't show any negative effect on the yield of addition reaction products (Table 2, entries 3). Platinacycle **4** is demonstrated to be an excellent catalyst for 1,2-addition reaction of arylboronic acids with aldehydes with relatively broad substrate scope.

**Table 1.2** Platinacycle **4**-Catalyzed Addition Reactions of Arylboronic Acids with Aldehydes[a]




| Entry | Ar-$B(OH)_2$ | RCHO | Yield(%)[b] |
|---|---|---|---|
| 1 |  |  | 95 |
| 2 |  |  | 91 |
| 3 |  |  | 86 |
| 4 |  |  | 93 |
| 5 |  |  | 83 |
| 6 |  |  | 86[c] |
| 7 |  |  | 83 |
| 8 |  |  | 80 |
| 9 |  |  | 79 |
| 10 |  |  | 78 |

a. Reaction conditions: aldehydes (1.0 equiv), arylboronic acid (2.0 eq), 4 (2-5%), toluene (2ml), $K_3PO_4$ (1.0 equiv), 60-80 $^oC$. b. Isolated yields (average of two runs), c. addition product: coupling product = 12:1.

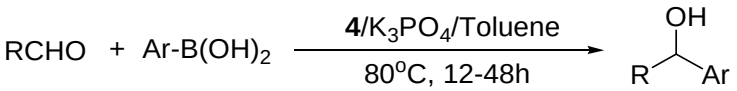
## 1.4 Platinacycle 4-Catalyzed Addition Reactions of Arylboronic Acids with Aldehydes by Low Catalyst Loadings

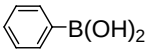
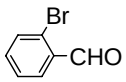
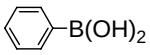
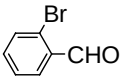
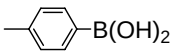
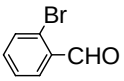
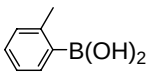
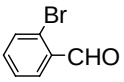
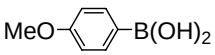
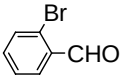
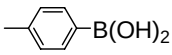
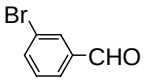
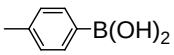
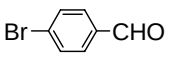
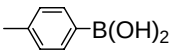
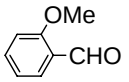
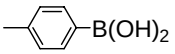
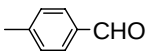
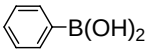
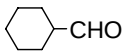
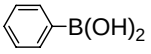
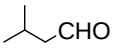
One of the main shortcomings in transition metal-catalyzed addition reactions of arylboronic acids with aldehydes is the high catalyst loading, typically 3% or more.[1-3,5] The reductive elimination which happened after the transmetalation would generate zero valent transition metal complexes or metal particles which cannot catalyze addition. The reluctance of diorgano Pt complexes to undergo reductive elimination, which suggested the catalyst decomposition could be minimized, raised the possibility to use a low catalyst loading for the addition reactions. We next turned our attention to test the possibility to use the lower catalyst loading for the addition reactions. We thus employed the 0.1-0.05% catalyst loading for the addition reactions of arylboronic acids with aldehydes with 3 equivalents of $K_3PO_4$ as base, the result are listed in the Table 1.3. As expected, such low catalyst loading still catalyzed the addition reactions of arylboronic acids with aldehydes, but with obvious decrease of isolated yields. When we used 0.01% catalyst loading, only 23% of conversion of the aldehydes could be obtained. We initially thought that the arylboronic acids contain a small amount of the impurity which can deactivate the catalyst.[10d] Based on this consideration, we used the phenylboroxine $(PhBO)_3$ in place of phenylboronic acid, which was obtained by dehydration of the commercially available phenylboronic acid by azeotropic removal of water from its toluene solution and purified by washing the crude boroxine repeatedly with hexane. [10d] At this time, we used 2-bromobenzaldehyde and phenylboroxine as starting materials with 0.02% catalyst loading and 3 equivalence of $K_3PO_4$ as base to set up the reaction again. The conversion of aldehydes in the reaction can be increased to 90% with 8% cross-coupling product

based on $^{1}H$ NMR. However, exist of cross-coupling product suggested that some platinacycle catalysts have decomposed which is harmful to catalysis with a low catalyst loading.

After further investigating the reaction, we found that if we use **3** equivalents of base, we cannot obtain ideal isolated yields for the addition products, even with 3% catalyst loading. There are still 5-14% of byproducts observed. We isolated the major byproducts and characterized them as ketones via $^{1}H$ and $^{13}C$ NMR. We realized that the excess amount of base might help the oxidation of the addition reaction products to ketones, a reaction which is known as the Meerwein-Ponndorf-Verley-Oppenauer reaction (Scheme 1.2). We then reexamined our reactions with the low catalyst loading with one equivalent of base. The expected addition reaction products were obtained with very small amounts of ketones byproducts being observed. The results are listed in Table 1.4. Under this reaction condition, we can obtain good to excellent yields for all aldehydes and arylboronic acids even with a 0.01% catalyst loading (Table 1.4, entry 4). To the best of our knowledge, the lowest catalyst loading to obtain a good isolated yield in this field was 0.25%.[6] Our 0.01% catalyst loading thus represents an unprecedented low amount.

**Table 1.3** Low Catalyst Loading of Platinacycle **4**-Catalyzed Addition Reactions of Arylboronic Acids with Aldehydes with 3 equiv Base[a]




| Entry | Ar-B(OH)$_2$ | RCHO | Cat. Loading | Yield(%)[b] | Ketone(%)[c] |
|---|---|---|---|---|---|
| 1 |  |  | 0.1 | 90 | <5 |
| 2 |  |  | 0.05 | 69 | <5 |
| 3 |  |  | 0.05 | 73 | 10 |
| 4 |  |  | 0.1 | 68[d] | 7 |
| 5 |  |  | 0.05 | 69 | 18 |
| 6 |  |  | 0.1 | 83 | <5 |
| 7 |  |  | 0.05 | 82 | <5 |
| 8 |  |  | 0.1 | 75 | 14 |
| 9 |  |  | 0.1 | 64 | 32 |
| 10 |  |  | 0.1 | 65 | 6 |
| 11 |  |  | 0.1 | 69 | 16 |

a. Reaction conditions: aldehydes (1.0 equiv), arylboronic acid (2.0 eq), **4** (2-5%), toluene (2ml), $K_3PO_4$ (3.0 equiv), 60-80 $^oC$. b. Isolated yields, c. addition product: coupling product = 12 : 1. d. 87% conversion.

**Scheme 1.2** Proposed Mechanism for the Formation of Ketone

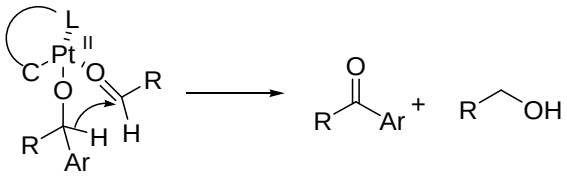
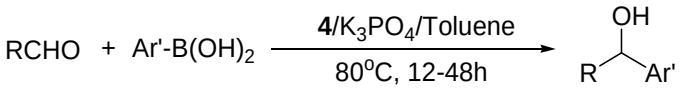
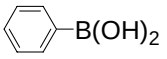
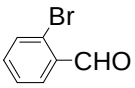
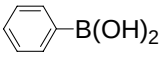
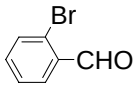
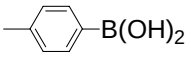
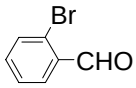
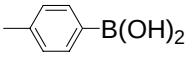
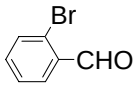
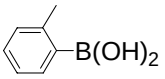
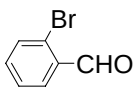
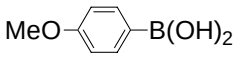
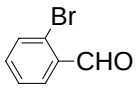
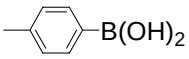
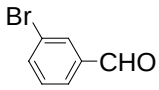
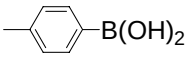
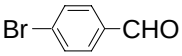
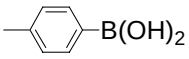
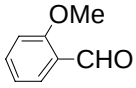
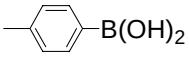
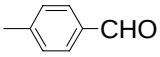
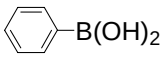
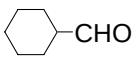
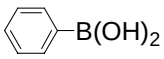
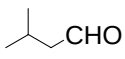


**Table 1.4** Low Catalyst Loading of Platinacycle **4**-Catalyzed Addition Reactions of Arylboronic Acids with Aldehydes with 1 equiv base[a]



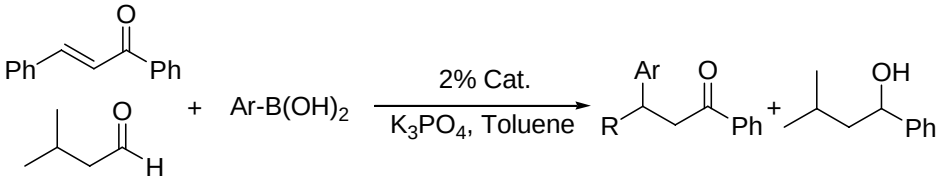

| Entry | Ar-B(OH)$_2$ | RCHO | Cat. Loading(%) | Yield(%)[b] |
|---|---|---|---|---|
| 1 |  |  | 0.1 | 90 |
| 2 |  |  | 0.05 | 80 |
| 3 |  |  | 0.05 | 85 |
| 4 |  |  | 0.01 | 81 |
| 5 |  |  | 0.05 | 87 |
| 6 |  |  | 0.05 | 86 |
| 7 |  |  | 0.05 | 84[c] |
| 8 |  |  | 0.05 | 82[d] |
| 9 |  |  | 0.1 | 75 |
| 10 |  |  | 0.1 | 64 |
| 11 |  |  | 0.1 | 65 |
| 12 |  |  | 0.1 | 74 |

a. Reaction conditions: aldehydes (1.0 equiv), arylboronic acid (2.0 eq), 4 (2-5%), toluene (2ml), $K_3PO_4$ (1.0 eq), 60-80 $^oC$. b. Isolated yields. c. There are addition product: coupling product = 15:1 in the crude product based on $^1H$ NMR. d. There are addition product: coupling product = 8:1 in the crude product based on $^1H$ NMR.

## 1.5 Platinacycle 4-Catalyzed Addition Reactions of Arylboronic Acids with α,β-Unsaturated Aldehydes.

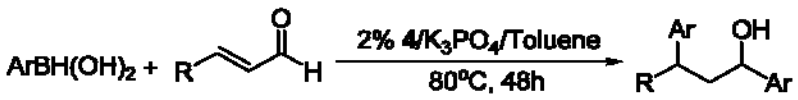
We have also employed **4** as the catalyst for the competitive addition reaction of phenylboronic acid with chalcone and 3-methylbutannal.[14b,14d,14e,22] We found that with platinacycle **4** as catalyst, the addition reaction exclusively occurred at the chalcone while with palladacycle **3** as the catalyst almost 1 : 1 ratio of 1,4-addition and 1,2-addition produces were observed (Scheme 3). Such a regioselectivity difference could be explained by the fact that platinum is softer than palladium, which the latter can activate the aldehyde carbonyl group better. These results suggested that platinacycle **4** could be an excellent catalyst for a new addition reaction sequence of Michael addition followed by 1,2-addition. We have thus explored the tandem reaction of arylboronic acids with α,β-unsaturated aldehydes and our results are listed in Table 8. Our study showed that the tandem reaction occurred smoothly, and double addition reaction products were obtained in good yields. To our knowledge, previously reported addition reactions of arylboronic acids with enals either afforded 1,2-addition product, allylic alcohols, or 1,4-addition product, β-arylated aldehydes;[13a,13b,13e,14d,22-23] our results represent the first examples that arylboronic acids add to α,β-unsaturated aldehydes successively to form 1,3-diaryl-1-propanols.[24]

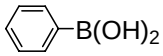
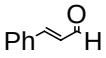
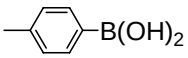
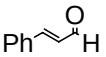
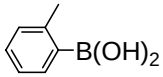
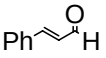
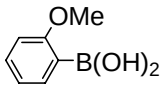
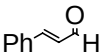
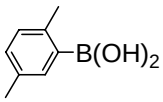
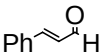
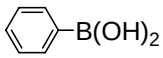
**Scheme 1.3** 1,2-Addition vs. 1,4-Addition Reactions




| | | | |
|---|---|---|---|
| Palladacycle 3: r.t. 20 h | 55 | : | 45 |
| Platinacycle 4: 80$^{o}$C 20h | >99 | : | <1 |

**Table 1.5** Tandem Reaction Catalyzed by Platinacycle **4**




| Entry | Ar-B(OH)$_2$ | R-CHO | Yield(%)[b] |
|---|---|---|---|
| 1 |  |  | 86 |
| 2 |  |  | 80 |
| 3 |  |  | 66 |
| 4 |  |  | 57 |
| 5 |  |  | 76 |
| 6 |  |  | 63 |

a. Reaction conditions: aldehydes (1.0 equiv), arylboronic acid (3.0 eq), 4 (2-5%), toluene (2ml), $K_3PO_4$ (1.0 - 3.0 equiv), 60-80 $^oC$. b. Isolated yields

In summary, we demonstrated that readily available, air/moisture-stable platinacycle **4** was a highly efficient catalyst for 1,2-addition reactions of arylboronic with aldehydes, with an unprecedented low catalyst loading for such addition reactions.

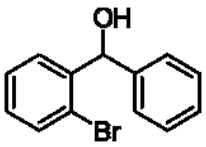
## 1.6 Experimental Section

General: NMR spectra were recorded on Varian 300MHz or 600MHz spectrometers. Elemental analysis was carried out by Altantic Microanalysis, Inc., Norcross, GA. All yields reported refer to isolated yields unless otherwise indicated, and the product purity was estimated to be greater than 95% as determined by $^1$H NMR. Compounds described

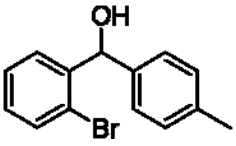
in the literature were characterized by comparison of their $^{1}H$ NMR and $^{13}C$ NMR spectra to reported data.

Toluene was purified by the column purification system of Innovative Technology. Arylboronic acids were obtained as gifts from Frontier Scientific, Inc. The orthoplatinum complexes was prepared according to the reported method.[12a] Other chemical reagents were purchased from Strem Chemicals, Aldrich or Alpha Aesar and used directly.

**General procedure for Platinacycle 4-catalyzed 1,2-addition reactions of arylboronic acids with aldehydes:** To a vial containing aldehyde (0.5 mmol), arylboronic acid (0.75 - 1.0 mmol), $K_3PO_4$ (0.5 - 1.5 mmol) and platinacycle **4** (0.0025-0.00005 mmol) was added toluene (2.0 ml). After the mixture was stirred at 60-80 $^{o}C$ for 12-24 hrs, the reaction was quenched by adding small amount of water. Column chromatography on silica gel with diethyl ether/hexane afforded the 1,2-addition product.

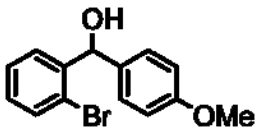



**(2-Bromophenyl)(phenyl)methanol** $^{1}H$ NMR ($CDCl_3$, 600 MHz) δ 7.58 (1H, d, J = 7.8 Hz), 7.53 (1H, d, J = 7.8 Hz), 7.40 (2H, d, J = 7.2 Hz), 7.34 (3H, m), 7.28 (1H, t, J = 7.2 Hz), 7.15 (1H, t, J = 7.8 Hz) , 6.20 (1H, s) , 2.38 (1H, s). $^{13}C$ NMR ($CDCl_3$, 150 MHz) δ 142.43, 142.07, 132.80, 132.75, 129.06, 128.43, 127.73, 127.69, 127.02, 122.75, 74.71, 74.65.

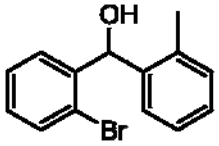



**(2-Bromophenyl)(*p*-tolyl)methanol** $^{1}H$ NMR ($CDCl_3$, 600 MHz) δ 7.56 (1H, d, J = 6.6 Hz), 7.48 (1H, d, J = 7.8 Hz), 7.29 (1H, t, J = 7.8 Hz), 7.10 (3H, d, J = 7.8 Hz), 6.06 (1H, s), 2.64 (1H, br), 2.30 (1H, m). $^{13}C$ NMR ($CDCl_3$, 150 MHz) δ 142.52, 139.12, 137.37, 132.71, 132.65, 130.45, 129.07, 128.87,

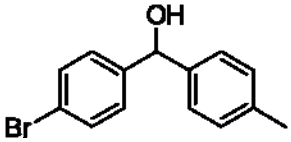
128.24, 128.18, 127.58, 126.98, 122.58, 74.53, 74.46, 21.13, 21.07.



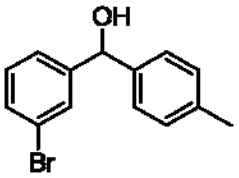

**(2-Bromophenyl)(4-methoxyphenyl)methanol** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.63 (1H, d, J = 8.4 Hz), 7.52 (1H, d, J = 7.8 Hz), 7.34 (1H, t, J = 7.8 Hz), 7.28 (2H, t, J = 9.0 Hz), 7.13 (2H, t, J = 7.8 Hz), 6.07 (1H, s), 3.77 (3H, s). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 158.87, 142.59, 134.29, 132.63, 128.77, 128.37, 128.35, 128.34, 128.02, 127.51, 122.47, 113.68, 74.21, 74.18, 55.09.




**(2-Bromophenyl)(*o*-tolyl)methanol** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.56 (1H, d, J = 7.8 Hz), 7.34 (1H, d, J = 7.8Hz), 7.29 (2H, d, J = 6.0Hz), 7.23-7.14 (4H, m), 6.28 (1H, d, J = 4.2Hz), 2.29 (3H, s), 2.26 (1H, d, J = 4.8Hz). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 141.78, 139.84, 136.02, 132.85, 130.47, 129.20, 128.82, 127.78, 127.60, 126.29, 126.07, 123.61, 72.13, 19.17.

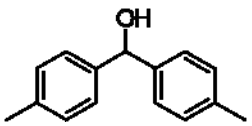



**(4-Bromophenyl)(*p*-tolyl)methanol** $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.43(2H, d, J = 11.4 Hz), 7.22 (4H, t, J = 8.1 Hz), 7.13 (2H, d, J = 7.8 Hz), 5.73 (1H, s), 2.32 (1H, s). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 142.82, 140.45, 137.61, 131.43, 129.29, 128.08, 126.46, 121.22, 75.41, 21.09.

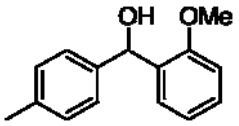



**(3-Bromophenyl)(*p*-tolyl)methanol** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.52 (1H, s), 7.35 (1H, d, J = 7.8 Hz), 7.24 (1H, d, J = 7.8 Hz), 7.19 (2H, d, J = 7.8 Hz), 7.16 (1H, d, J = 7.8 Hz), 7.13 (2H, d, J = 7.8 Hz), 5.69 (1H, s), 2.42 (1H, br) 2.32 (3H, s). $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 146.18,

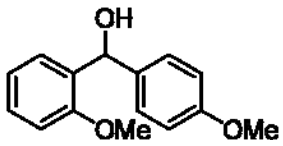
140.34, 137.70, 130.53, 130.36, 130.09, 129.89, 129.47, 129.36, 129.26, 126.68, 126.47, 125.13, 124.94, 122.60, 75.42, 21.16.



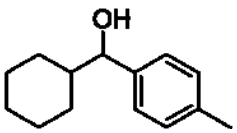

**Di*p*-tolylmethanol.** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.24 (4H, d, J = 8.4 Hz), 7.12 (4H, t, J = 7.8 Hz), 5.75 (1H, s). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 141.07, 137.07, 129.08, 126.39, 75.87, 21.06.




**(2-Methoxyphenyl)(*p*-tolyl)methanol** $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.27 - 7.22 (4H, m), 7.10 (2H, d, J = 8.1 Hz), 6.94-6.89 (1H, m), 6.86-6.83 (1H, m), 6.00 (1H, d, J = 4.5 Hz), 3.76 (3H, s), 3.07 (1H, d, J = 4.5 Hz), 2.31 (3H, s). $^{13}$C NMR ($CDCl_3$, 75 MHz) 158.73, 156.67, 135.45, 132.14, 128.59, 127.81, 127.63, 120.74 113.54, 110.68, 71.91, 55.29, 21.04.

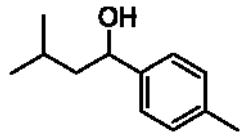



**(2-Methoxyphenyl)(4-methoxyphenyl)methanol** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.29 (2H, d, J = 8.4 Hz), 7.25 - 7.23 (2H, m), 6.94 (1H, t, J = 7.8 Hz), 6.88 (1H, d, J = 7.8 Hz), 6.85 (1H, d, J = 8.4 Hz), 6.01 (1H, d, J = 5.4 Hz), 3.80 (3H, s), 3.78 (3H, s), 2.96 (1H, d, J = 4.8 Hz). $^{13}$C NMR ($CDCl_3$, 150 MHz) 156.58, 140.26, 136.63, 132.00, 128.77, 128.51, 127.64, 126.43, 120.67, 110.59, 71.85, 55.39, 55.22.

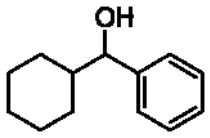



**Cyclohexyl(*p*-tolyl)methanol** $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.18 -7.11 (4H, m), 4.29 (1H, br), 2.33 (1H, s), 1.93 (1H, br), 1.72 (1H, br), 1.64 – 1.58 (3H, m), 1.38 - 1.32 (1H, br), 1.25 - 0.82 (5H, m). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 140.62, 136.91, 128.79, 126.51, 79.16, 44.83, 29.23,

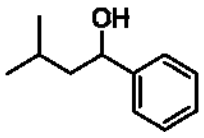
28.89, 26.38, 26.04, 25.96, 21.04.



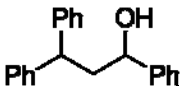

**3-Methyl-1-p-tolylbutan-1-ol** $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.23 -7.12 (4H, m), 4.68 (1H, br), 2.32 (1H, s), 1.96 (1H, br), 1.70-1.64 (2H, m), 1.4 -1.45 (1H, m), 0.94-0.91 (6H, br). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 142.19, 137.05, 129.06, 125.79, 72.52, 48.18, 24.75, 23.00, 22.26, 21.03.




**Cyclohexyl(phenyl)methanol** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.34 -7.25 (5H, m), 4.34 (1H, d, J = 6.6 Hz), 1.98 (1H, d, J = 12.6 Hz), 1.94 (1H, s), 1.75 (1H, d, J = 13.2 Hz), 1.66 - 1.58 (3H, m), 1.36 (1H, d, J = 12.6 Hz), 1.25 - 0.87 (5H, m). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 143.56, 128.13, 127.35, 126.60, 79.33, 44.87, 29.23, 28.79, 26.37, 26.04, 25.96.

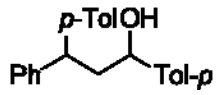



**3-Methyl-1-phenylbutan-1-ol** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.36 - 7.33 (3H, m), 7.29 - 7.22 (2H, m), 4.73 (1H, br), 1.90 (1H, br), 1.75 - 1.66 (2H, m), 1.52 - 1.47 (1H, m), 0.95 (3H, d, J = 2.4 Hz), 0.94 (3H, d, J = 3.0 Hz). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 145.16, 128.43, 127.45, 125.82, 72.72, 48.29, 24.74, 23.09, 22.21.

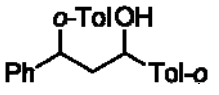



**1,3,3-Triphenylpropan-1-ol** $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.32-7.14 (16H, m), 4.44 (1H, dd, J = 7.2 Hz), 4.11 (1H, dd, J = 7.2 Hz), 2.54-2.34 (2H, m), 1.99 (1H, br). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 144.60, 144.55, 144.11, 128.52, 128.47, 127.94, 127.76, 127.64, 126.26, 126.18, 125.91,

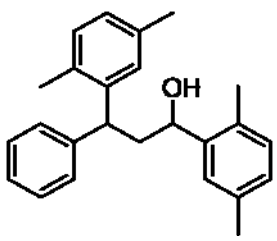
72.22, 47.45, 44.67.




**3-Phenyl-1,3-di*p*-tolylpropan-1-ol** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.25-7.20 (4H, m), 7.16-7.06 (9H, m), 4.43 (1H, dt, J = 5.4 Hz), 4.05 (1H, dd, J = 17.4 Hz, J = 13.2 Hz), 2.55 – 2.35 (2H, m), 7.18 - 7.14 (3H, m), 6.79 (2H, d, J = 8.4 Hz), 4.77 (1H, t, J = 7.2 Hz), 2.33 (3H, s), 2.29 (3H, d, J = 5.4 Hz), 1.85 (1H, br). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 144.93, 144.51, 141.64, 141.60, 137.31, 135.71, 135.65, 129.22, 129.15, 128.49, 128.44, 127.85, 127.80, 127.72, 127.64, 126.14, 126.08, 125.93, 125.91, 72.18, 72.10, 47.11, 47.08, 44.63, 21.10, 20.96.

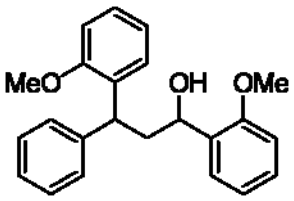



**3-Phenyl-1,3-di*o*-tolylpropan-1-ol** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.48 (1H, t, J = 7.8 Hz), 7.37-7.32 (1H, m), 7.28-7.06 (10H, m), 4.77-4.72 (1H, m), 4.59-5.56 (0.75H, m), 4.42-4.40 (0.3H, m), 2.38 (1H, t, J = 6.6Hz), 2.35 ( 2H, s), 2.19 (1H, s), 2.10 (2H, s), 1.89 (1H, s). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 144.63, 143.57, 142.94, 142.44, 141.83, 136.74, 136.51, 134.42, 130.64, 130.54, 130.42, 130.38, 128.49, 128.38, 127.90, 127.22, 126.98, 126.34, 126.32, 126.28, 126.18, 126.04, 125.99, 125.94, 125.18, 125.10, 68.57, 68.15, 44.45, 44.24, 43.38, 42.75, 19.96, 19.77, 18.79, 18.36.




**1, 3-Bis(2,5-dimethylphenyl)-3-phenylpropan-1-ol** $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.26 (3H, m), 7.23-7.20 (2H, m), 7.18-7.11 (2H, m), 7.06 – 6.89 (4H, m), 4.74 – 4.68 (1H, m), 4.54 (0.5H, t, J = 8.1 Hz), 4.40 (0.5H, t, J = 8.1 Hz), 2.37-2.28 (9.5H,

m), 2.16 (1.5H, s), 2.07 (1.5H, s), 1.85 (1.5H, s). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 144.74, 143.65, 142.86, 142.81, 142.33, 141.43, 135.77, 135.23, 135.20, 133.63, 133.29, 131.16, 131.09, 130.5, 130.37, 130.31, 128.49, 128.35, 128.32, 127.90, 127.66, 127.03, 127.87, 126.78, 126.08, 125.92, 125.80, 125.70, 68.48, 68.14, 44.54, 44.36, 43.29, 42.73, 21.24, 21.18, 21.07, 19.47, 19.35, 18.22, 17.91.




**1,3-bis(2-methoxyphenyl)-3-phenylpropan-1-ol** $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.12 (9H, m), 6.96-6.80 (4H, m), 4.73-4.64 ( 2H, m), 3.78 (1H, s), 3.77 (1H, s), 2.82 (0.3H, d, J = 7.2 Hz), 2.67 (0.7H, d, J = 7.2 Hz), 2.32-2.58 (2H, m). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 157.17, 156.77, 156.52, 156.29, 144.98, 143.99, 133.66, 132.53, 128.51, 128.23, 128.14, 128.10, 128.05, 127.60, 110.77, 110.59, 110.41, 110.31, 69.72, 68.87, 55.53, 55.34, 55.07, 42.62, 42.33, 39.93, 39.70.

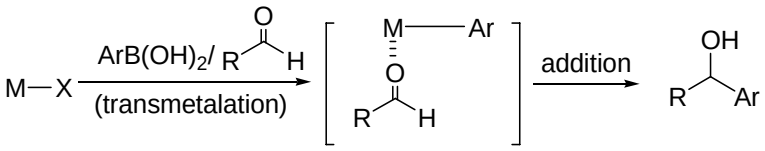
# Chapter 2. A Non-Transmetalation Pathway for Anionic Four-Electron Donor-Based Palladacycle-Catalyzed Addition Reactions of Arylborons with Aldehydes

## 2.1 Introduction

We demonstrated that orthoplatinated triarylphosphite catalyst is an excellent catalyst for the addition reaction in Chapter 1. However, platinum is a weaker Lewis acid compared to other transition metals like Rh and Pd and thus shows a lower catalytic activity on addition reactions. Therefore, relatively harsh reaction conditions such as 80 $^{o}$C and long reaction time are necessary. In other words, to minimize the reductive elimination, we sacrificed the catalytic activity by choosing platinacycle as catalyst. Since palladium is stronger Lewis acids than platinum, if the reductive elimination of palladium catalyst can be minimized, we may develop much more efficient transition metal catalyst for addition reactions.

Transmetalation of organometallic reagents with ArPd(II)X(Ln) complexes comprises one of the key steps in Pd-catalyzed cross-coupling reactions such as the Kumada coupling, the Stille coupling and the Suzuki coupling.[25,26] In these coupling reactions, it is desirable for transmetalation to occur. Transmetalation of organoboronic acids with transition metal catalysts has also been considered as a key step in transition metal-catalyzed addition reactions of arylboronic acids with aldehydes, imines and α,β-unsaturated ketones/aldehydes/esters (Scheme 2.1).[14d,14e,27,13b,13f,21,28,29]

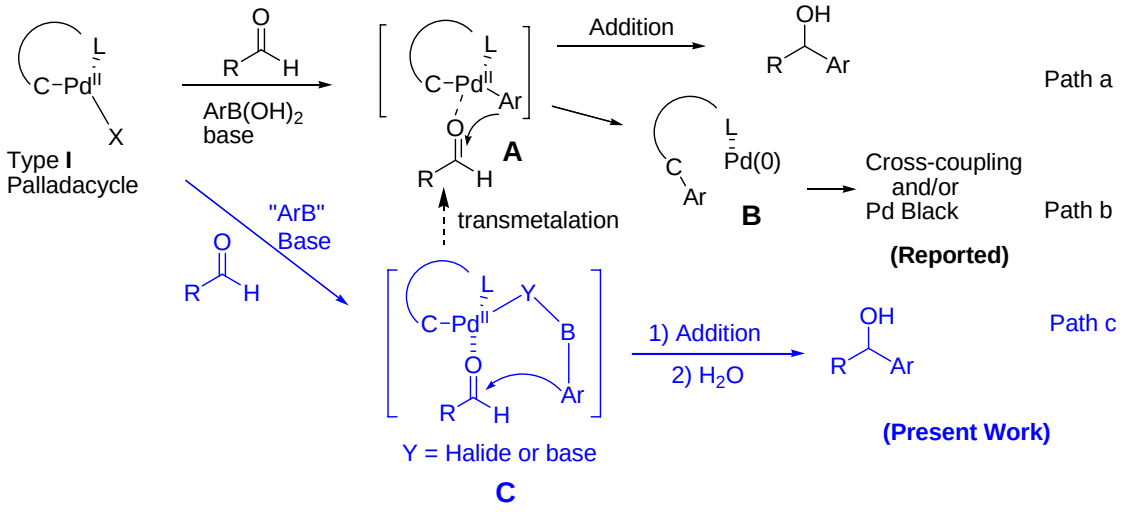
**Scheme 2.1** Transition Metal-Catalyzed Addition Reactions of Arylboronic Acid with Aldehydes




M = Rh(I)/(II), Pd(II), Pt(II), Ni(0)/Ni(II), Cu(II), Fe(III), Co(II)

In the early study from our group on employing anionic four-electron donor-based (Type I) palladacycles,[30] which are readily available and air/moisture-stable, as catalysts for addition reactions,[8-9,31] the transmetalation of arylboronic acids with Pd-X to form **A** was also considered to be a key step (Scheme 2.2, Path a). As described in Chapter 1, during our early study, we were bothered by the decomposition of Pd(II) catalyst to Pd(0) species **B** via reductive elimination of **A** (Scheme 2.2, Path b)**,** which resulted in high catalyst loadings (3 mol% or more) and limited the scope of substrates/arylboronic acids. Based on the consideration that contacts between Type I palladacycles and arylboronic acids should occur prior to the transmetalation between them,[32] *i.e.,* complexes such as **C** might be formed prior to the formation of **A**, we hypothesized a new reaction pathway for Type I palladacycle-catalyzed addition reactions: the addition reactions (aryl transferring) might take place at this stage to afford addition product without the occurrence of transmetalation (Scheme 2.2, Path c)**.** Achieving such addition reactions (aryl transferring) without transmetalation could prevent palladacycle catalysts from decomposition and thus offer us new catalysis opportunities such as low catalyst loading catalysis, expanded substrates/nucleophile scope and new bond-forming reactions. In this chapter, we report our results to establish such a possibility, specifically Type I palladacycle-catalyzed addition reactions of arylboroxines with aldehydes, with unprecedented low catalyst loading and expanded nucleophile scope.

**Scheme 2.2** Mechanistic Considerations for Type I Palladacycle Catalyzed Addition Reactions of Arylborons with Aldehydes.




## 2.2 Anionic Four-Electron Donor-Based Palladacycle-Catalyzed Addition Reactions of Arylborons with Aldehydes in Anhydrous Conditions

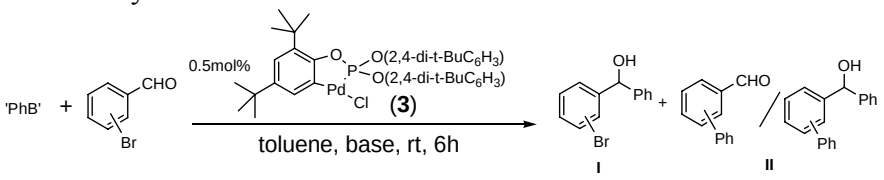
It has been established that transmetalation of organoboron compounds with Pd–X complexes would be very slow in the absence of species such as $H_2O/OH^-$, $ROH/OR^-$,[25,33] we surmised that conditions without these species such as an anhydrous condition might achieve the addition reaction without the occurrence of transmetalation. We thus began our study by determining the feasibility to achieve the addition reaction under the anhydrous condition. Dried arylboronic acids (arylboroxines)[15a] and dried $K_3PO_4$ were used. Bromobenzaldehydes were chosen as substrates since they contain both the addition reaction acceptor (aldehyde carbonyl group) and cross-coupling acceptor (C–Br moiety). The observation of Pd black and/or detection of cross-coupling products would indicate the formation of Pd(0) species. We first examined the reaction of 2-bromobenzaldehyde with phenylboroxine and dried $K_3PO_4$ (1 equiv) with Type I

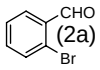
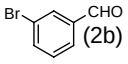
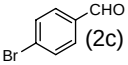
palladacycle **3** as the catalyst. We were very pleased to find that the addition reaction occurred smoothly, with no cross-coupling reaction product being observed (Table 2.1, entries 1 and 2). In addition, no Pd black was observed for the reaction system even after three days. This was in sharp contrast to the results for the same reaction being carried out in the presence of water: significant amount of cross-coupling product was detected and Pd black was observed in less than 10 min (Table 2.1, entries 3–8). Similar trends were also observed with other bases, which were less effective than $K_3PO_4$ (Table 2.1, entries 9–13), and with 3-bromobenzaldehyde and 4-bromobenzaldehyde as substrates (Table 2.1, entries 14–21). These results showed that the addition reactions could indeed occur under anhydrous conditions and the catalyst decomposition was observed to be minimal.

The hypothesis of addition reactions taking place without the occurrence of transmetalation suggested that the decomposition of the palladacycle catalysts would not occur, even at elevated temperature. Thus, this nontransmetalation hypothesis implied that the catalyst loading could be lowered to an unprecedented level by using arylboroxines and dried bases, and previously unsuitable or unreactive arylboronic acids such as *o*-trifluoromethylcontaining arylboronic acids could be appropriate for the addition reactions. We tested such possibilities and our results are summarized in Table 2.2.. We found that 0.001–0.02 mol % catalyst loading was sufficient enough to effect the addition reactions of arylboroxines with aldehydes in high yields (Table 2.2, entries 1–17). We also found electron-deficient arylboroxines, generated from arylboronic acids such as *o*-trifluoromethyl-containing phenylboronic acids, were excellent nucleophiles (Table 2.2, entries 18–21). Further decreasing the catalyst loading was also tested and we

found excellent yield was obtained with the catalyst loading as low as 0.0005 mol % by

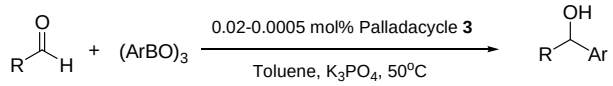
**Table 2.1** Palladacycle **3**-Catalyzed Reactions of Phenylboronic Acid/Phenylboroxine with Bromobenzaldehydes[a]

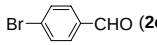
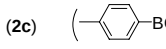
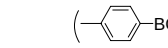
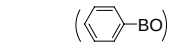
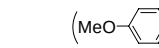
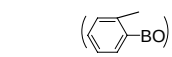
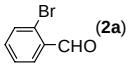
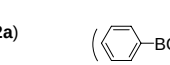
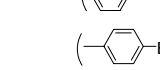
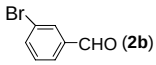
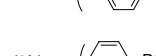
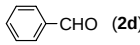
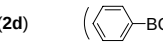
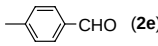
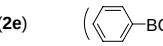
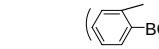
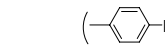
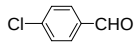
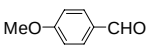
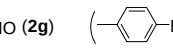
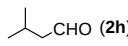
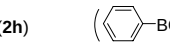
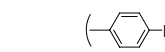
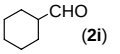
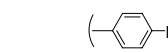
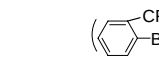
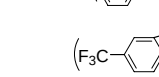
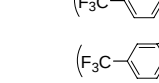
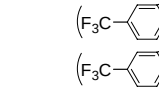
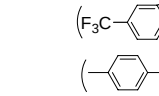
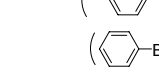
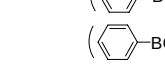



| entry | Br–⟨⟩–CHO | 'PhB' | base(equiv) | $H_2O$ (equiv) | conv. (%) | ratio of I:II[b] |
|---|---|---|---|---|---|---|
| 1 |  (2a) | $(PhBO)_3$ | $K_3PO_4$ (A, 1) | - | 78 | 100:0 |
| 2 | (2a) | $(PhBO)_3$ | $K_3PO_4$ (A, 3) | - | 81 | 100:0 |
| 3 | (2a) | $PhB(OH)_2$ | $K_3PO_4$ (B, 3) | - | 95 | 85:15 |
| 4 | (2a) | $PhB(OH)_2$ | $K_3PO_4$ (B, 1) | - | 71 | 39:61 |
| 5 | (2a) | $PhB(OH)_2$ | $K_3PO_4$ (A, 1) | - | 83 | 77:23 |
| 6 | (2a) | $PhB(OH)_2$ | $K_3PO_4$ (A, 3) | - | 75 | 95:5 |
| 7 | (2a) | $(PhBO)_3$ | $K_3PO_4$ (B, 3) | 1 | 77 | 83:17 |
| 8 | (2a) | $(PhBO)_3$ | $K_3PO_4$ (A, 3) | 1 | 71 | 82:18 |
| 9[c] | (2a) | $(PhBO)_3$ | $K_2CO_3$ (A, 1) | - | 48 | 100:0 |
| 10[c] | (2a) | $(PhBO)_3$ | $K_2CO_3$ (A, 1) | 1 | 89 | 53:47 |
| 11[c] | (2a) | $(PhBO)_3$ | $Na_2CO_3$ (A, 1) | - | 15 | 100:0 |
| 12[c] | (2a) | $(PhBO)_3$ | KOAc (A, 1) | - | 3 | - |
| 13[c] | (2a) | $(PhBO)_3$ | KF (A, 1) | - | 33 | 100:0 |
| 14 |  (2b) | $(PhBO)_3$ | $K_3PO_4$ (A, 3) | - | 40 | 99:1 |
| 15 | (2b) | $PhB(OH)_2$ | $K_3PO_4$ (B, 1) | - | 67 | 14:86 |
| 16 | (2b) | $(PhBO)_3$ | $K_3PO_4$ (A, 3) | 1 | 70 | 38:62 |
| 17 | (2b) | $(PhBO)_3$ | $K_3PO_4$ (A, 3) | 3 | 80 | 40:60 |
| 18 |  (2c) | $(PhBO)_3$ | $K_3PO_4$ (A, 3) | - | 47 | 99:1 |
| 19 | (2c) | $PhB(OH)_2$ | $K_3PO_4$ (B, 1) | - | 60 | 50:50 |
| 20 | (2c) | $(PhBO)_3$ | $K_3PO_4$ (A, 3) | 1 | 84 | 36:64 |
| 21 | (2c) | $(PhBO)_3$ | $K_3PO_4$ (A, 3) | 3 | 90 | 40:60 |
| 22 | (2c) | $(PhBO)_3$ | $K_3PO_4$ (A, 3) | - | 0 | -[d] |
| 23 | (2a) | $(PhBO)_3$ | $K_3PO_4$ (A, 0) | - | 0 | - |
| 24 | (2a) | $(PhBO)_3$ | $K_3PO_4$ (A, 0.25) | - | 21 | 100:0 |
| 25 | (2a) | $(PhBO)_3$ | $K_3PO_4$ (A, 0.50) | - | 44 | 100:0 |
| 26 | (2a) | $(PhBO)_3$ | $K_3PO_4$ (A, 0.75) | - | 63 | 100:0 |

[a]Reaction conditions: aldehyde (1.0 equiv), phenylboronic acid (2.0 equiv) or phenylboroxine (0.67 equiv), toluene (2 mL), base (1 or 3 equiv, A: ground and dried, B: ground), room temperature, 6 h. [b]Based on 1H NMR or GC–MS. [c]1 mol % catalyst loading in 3 h. [d]No palladacycle **1** was used, rt or 50 $^oC$, 24 h.

**Table 2.2** Palladacycle **3**-Catalyzed Reactions of Arylboroxines with Aldehydes with Low Catalyst Loading[a]




| Entry | RCHO | $(ArBO)_3$ | Catalyst Loading(%) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 |  (**2c**) |  | 0.01 | 72 | 89[c] |
| 2 | **2c** |  | 0.01 | 24 | 91 |
| 3 | **2c** |  | 0.01 | 24 | 93 |
| 4 | **2c** |  | 0.01 | 24 | 86 |
| 5 | **2c** |  | 0.01 | 24 | 91 |
| 6 |  (**2a**) |  | 0.01 | 24 | 90 |
| 7 | **2a** |  | 0.01 | 24 | 90 |
| 8 |  (**2b**) |  | 0.01 | 24 | 90 |
| 9 |  (**2d**) |  | 0.01 | 24 | 91 |
| 10 |  (**2e**) |  | 0.01 | 30 | 87 |
| 11 | **2e** |  | 0.01 | 30 | 89 |
| 12 | **2e** |  | 0.01 | 30 | 84 |
| 13 |  (**2f**) |  | 0.01 | 24 | 92 |
| 14 |  (**2g**) |  | 0.02 | 36 | 83 |
| 15 |  (**2h**) |  | 0.02 | 36 | 83 |
| 16 | **2h** |  | 0.02 | 30 | 81 |
| 17 |  (**2i**) |  | 0.02 | 30 | 82 |
| 18 | **2a** |  | 0.01 | 12 | 85[d] |
| 19 | **2a** |  | 0.01 | 12 | 90[d] |
| 20 | **2c** |  | 0.01 | 12 | 91[d] |
| 21 | **2e** |  | 0.01 | 12 | 83[d] |
| 22 | **2c** |  | 0.005 | 36 | 92 |
| 23 | **2c** |  | 0.001 | 60 | 91 |
| 24 | **2c** |  | 0.0005 | 24 | 83[e] |

[a]Reaction conditions: aldehydes (0.25 mmol), arylboroxines (0.67 mmol), base (1 or 3 eq), 50 °C. [b]Isolated yield. [c]Reaction was carried out at room temperature. [d]Reaction was carried out at 90 °C. [e]Reaction was carried out at 80 °C.

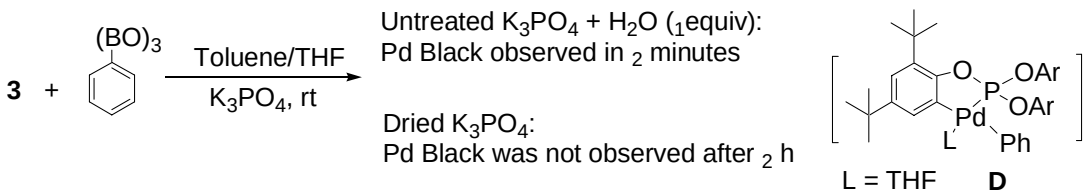
extending the reaction time and/or raising the temperature (Table 2.2, entries 22–24). To our knowledge, this is the lowest catalyst loading ever reported for such addition reactions. Compared to our previously reported platinacycle-catalyzed addition reactions of arylboronic acids with aldehydes, in which 0.01 mol % catalyst loading was achieved,[10a] our study described here apparently offered a catalysis protocol with unprecedentedly low catalyst loading and expanded nucleophile scope under milder reaction conditions.

## 2.3 Mechanism Studies on Palladacycle-Catalyzed Addition Reactions of Arylborons with Aldehydes in Anhydrous Conditions

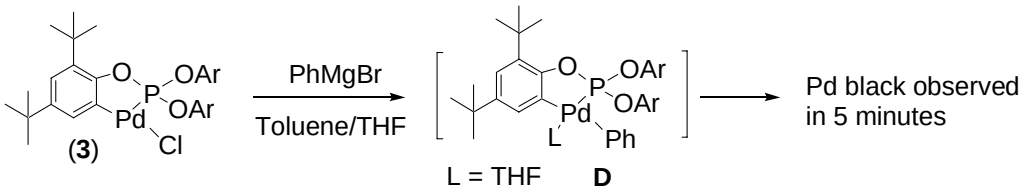
To support that the addition reaction under anhydrous condition occurred via the nontransmetalation pathway, we first excluded the possibility of phenylboroxine reacted with 4-bromobenzaldehyde in the absence of palladacycle **3** catalyst (Table 2.1, entry 22). We examined the addition reaction with different amounts of the base and found the presence of the base was vital to the addition reaction (Table 2.1, entries 23–26), suggesting that the base likely participated in the addition reaction via either **C** or transmetalation to form **A**. To understand whether $K_3PO_4$ facilitated the transmetalation of palladacycle **3** with phenylboroxine to form **A**, we tested the reaction of palladacycle **3** with phenylboroxine in the presence of $K_3PO_4$. We found while Pd black was observed in less than 2 min when this reaction was carried out in the presence of water, no Pd black formation was observed under anhydrous reaction condition (Scheme 2.3). This result suggested that the under anhydrous condition, either no transmetalation between palladacycle **3** and phenylboroxine occurred or the transmetalated intermediate **D** was

stable. We thus tested the reaction of palladacycle **3** with phenylmagnesium bromide, in which **D** was expected to be the intermediate. We found Pd black was observed in less than 5 min (Scheme 2.4), suggesting that the Pd(0) species formed from the transmetalation of palladacycle **3** with PhMgBr, **D**, should not be stable. We also carried out palladacycle **3**-catalyzed reaction of 2-bromotoluene with phenylboroxine and phenylboronic acid. We found the cross-coupling reaction of 2-bromotoluene and 2-bromoacetophenone with phenylboroxine occurred much slower under anhydrous condition than in the presence of $H_2O$ (Scheme 2.5). Because the oxidative addition and reductive elimination steps for these cross-coupling reactions did not involve the role of base (anhydride condition would only effect the transmetalation step), the low conversions observed for reactions under anhydrous condition suggesting that transmetalation between palladacycle **3** and phenylboroxine occurred very slowly under anhydrous condition. These results suggested that palladacycle **3**-catalyzed addition reactions of bromobenzaldehydes with phenylboroxine under anhydrous conditions were likely to have occurred without the transmetalation between Type I palladacycle **3** and phenylboroxines.

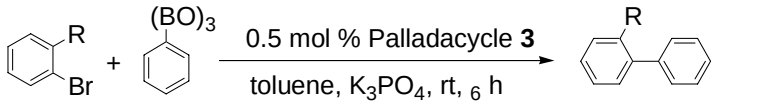
**Scheme 2.3** Reaction of Palladacycle **3** with Phenylboronic Acid/Phenylboroxine



**Scheme 2.4** Reaction of Palladacycle **3** with Phenylmagnesium Bromide



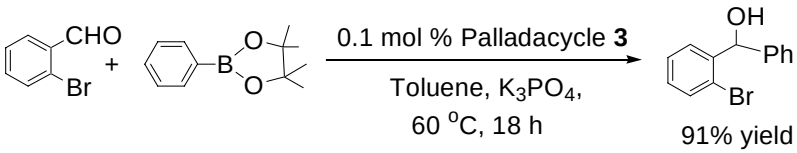

**Scheme 2.5** Palladacycle **3**-Catalyzed Reaction of 2-Bromoarenes with Phenylboronic Acid/Phenylboroxine




| | R = $CH_3$ | R = $COCH_3$ |
|---|---|---|
| Conversion: without adding $H_2O$: | < 3% | 2% |
| with adding $H_2O$ ($_1$equiv): | 73% | 50% |

The nontransmetalation pathway hypothesis suggested that other arylborons such as arylboronate esters should also be suitable nucleophile sources for the addition reaction in the absence of water.[7a,10t,34] We thus tested the use of pinacol phenylboronate for the addition reaction and found it indeed served as an excellent reagent for the addition reaction and the addition reaction product was obtained in a high yield (Scheme 6).

**Scheme 2.6** Palladacycle **3**-catalyzed addition reaction of pinacol phenylboronate with 2-bromobenzaldehyde.



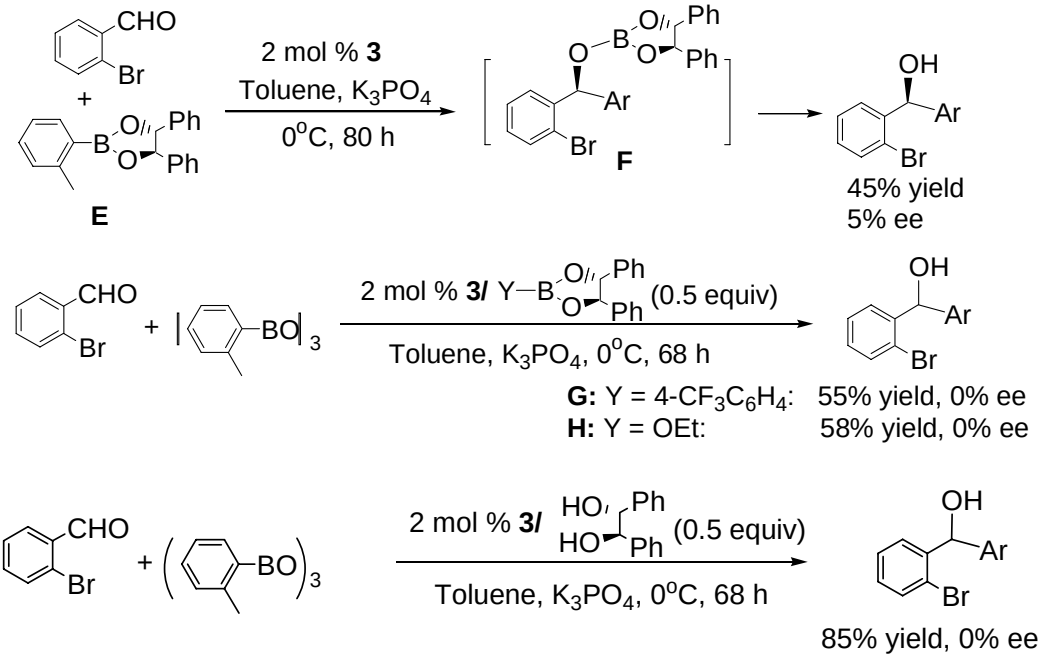

We then tested the use of optically active *o*-tolylboronate for the addition reaction. We reasoned that a racemic reaction product (0% ee) should be observed if the addition

reaction occurred with **A**, formed via transmetalation process, as the intermediate (Scheme 2.2, path a). On the other hand, a nonracemic reaction product (> 0% ee) might be formed if the addition reaction occurred without the occurrence of transmetalation (Scheme 2, path c). We examined the addition reaction of optically active *o*-tolylboronate **E** with 2-bromobenzaldehyde and found that the reaction occurred smoothly. As in the cases with arylboroxines as nucleophiles, no Pd black was observed. Importantly, a 5% ee was observed for the reaction product (Scheme 2.7). To exclude the possibility that optically active boronate **E** or borate **F** acted as chiral Lewis acids to induce the enantioselectivity, we tested the use of optically active boronate **G** and boronate **H**, analogues of **E** and **F**, as additives for the addition reaction of 2-bromobenzaldehyde with *o*-tolylboroxine (Scheme 2.7). No enantioselectivity was observed for the addition reaction with either optically active boronate **G** or borate **H** as the additive, suggesting that the enantioselectivity observed with **E** as the nucleophile was not due to the Lewis acid function of optically active boronate **E** or borate **F**. As no enantioselectivity was observed for the addition reactions of *o*-tolylboroxine with 2-bromobenzaldehyde in the presence of (R,R)-1,2-diphenyl-1,2-ethanediol (Scheme 2.7), our result with the use of optically active *o*-tolylboronate **E**, even though the observed ee% was low, suggested that the occurrence of transmetalation was unlikely for the addition reaction.

In summary, based on the hypothesis that the Type I palladacycle-catalyzed addition reactions of arylborons with aldehydes might occur without transmetalation between palladacycles and arylborons, we demonstrated that the Type I palladacycle-catalyzed addition reaction of arylboroxines/arylboronates with aldehydes occurred smoothly under anhydrous conditions. We found that Type I palladacycles could be long-lived under

anhydrous conditions. This new addition reaction mechanism hypothesis allowed us to use previously unused *o*-trifluoromethyl-containing arylboroxines as nucleophiles and to develop an unprecedentedly low catalyst loading protocol for the transition metal-catalyzed addition reaction of organoboron reagents with aldehydes. This new addition reaction pathway could be applicable for other transition metal-catalyzed addition reactions of organoboron reagents with carbonyl-containing compounds. Under the guidance of this new non-transmetalation mechanism, we further developed other transition metal-catalyzed addition reactions such as Rh(I)-catalyzed addition reaction of arylborons with ketones and Cu(I)-catalyzed addition reaction of arylboroxines with carbonyl-containing compounds, which will be discussed in following chapters.

**Scheme 2.7** Palladacycle **3**-Catalyzed Addition Reaction of Optically Active Phenylboronate with 2-Bromobenzalde



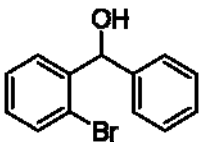
## 2.4 Experimental Section

**General**: NMR spectra were recorded on Varian 300MHz or 600MHz spectrometers. Elemental analysis was carried out by Altantic Microanalysis, Inc., Norcross, GA. High resolution mass spectra (HRMS) were acquired by Agilent G6520 Q-TOF mass spectrometer. All yields reported refer to isolated yields unless otherwise indicated, and the product purity was estimated to be greater than 95% as determined by $^{1}H$ NMR. Compounds described in the literature were characterized by comparison of their $^{1}H$ NMR and $^{13}C$ NMR spectra to reported data. New compounds were also characterized by element analysis or high resolution mass.

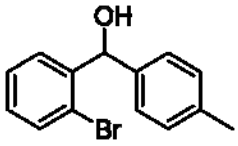
Arylboronic acids were obtained as gifts from Frontier Scientific, Inc. Arylboroxines were prepared by azeotropic distillation of arylboronic acids with dry toluene for 6 hours. The product purity was estimated to be greater than 95% as determined by $^{1}H$ NMR. Palladacycle **3** was prepared according to the reported method. The dried bases ($K_3PO_4$, $K_2CO_3$ and KF) were obtained by baking well-ground base powder at 140 $^{o}C$ under vacuum for 6 hours. Toluene was dried and freshly distilled with sodium prior to use. Other chemical reagents were purchased from Strem Chemicals, Aldrich or Alpha Aesar and used directly.

**General procedure for palladacycle 3-catalyzed addition reactions of arylboroxines with aldehydes:** To a vial containing aldehyde (0.25 mmol), arylboroxine (0.167 mmol), $K_3PO_4$ (0.75 mmol) and palladacycle **3** (0.00125-0.0000125 mmol) (palladacycle **3** was added in a toluene solution: 1 mg/mL solution of palladacycle **3** in toluene was freshly prepared and 1-40 μL of this solution was added to the reaction system by microsyringes) was added toluene (1 mL). After the mixture was stirred at 50-90 $^{o}C$ for 20-60 hours, the

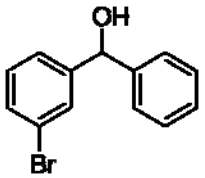
reaction was quenched by adding a small amount of water. Column chromatography on silica gel with ethyl acetate/hexane (v/v=1:10) afforded the alcohols.



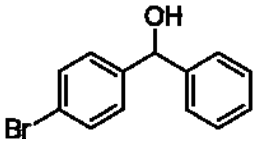

**(2-Bromophenyl)(phenyl)methanol:** $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.56 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 3H), 7.27-7.25 (m, 1H), 7.13 (t, *J* = 7.8 Hz,1H) , 6.16 (s, 1H) , 2.50 (s, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 142.5, 142.1, 132.8, 129.1, 128.4, 127.7, 127.7, 127.0, 122.8, 74.7 ppm.




**(2-Bromophenyl)(*p*-tolyl)methanol:** $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.2 Hz, 2H),7.12 (d, *J* = 7.8 Hz, 3H), 6.11 (d, *J* = 3.6 Hz, 1H), 2.43 (d, *J* = 3.6 Hz, 1H), 2.31 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 142.6, 139.2, 137.5, 132.8, 129.1, 128.9, 128.3, 127.6, 127.0, 122.7, 74.6, 21.1 ppm.

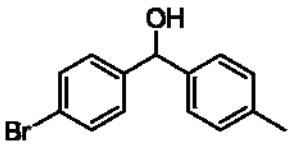



**(3-Bromophenyl)(phenyl)methanol:** $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.53 (s, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.33-7.31 (m, 4H), 7.28-7.25 (m, 2H), 7.16 (t, *J* = 7.8 Hz, 1H), 5.73 (d, *J* = 3.6 Hz, 1H), 2.47 (d, *J* = 3.0 Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 145.9, 143.1, 130.5, 130.0, 129.4, 128.6, 127.9, 126.5, 125.0, 122.6, 75.5 ppm.

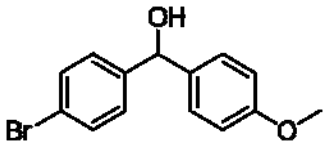



**(4-Bromophenyl)(phenyl)methanol:** $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.33-7.24 (m, 5H), 7.20 (d, *J* = 8.4 Hz, 2H), 5.71 (s, 1H), 2.50 (s, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 143.3,

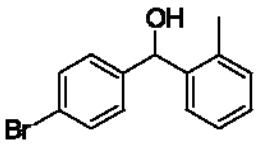
142.6, 131.5, 128.6, 128.1, 127.8, 126.5, 121.3, 75.5 ppm.



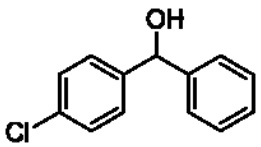

**(4-Bromophenyl)(*p*-tolyl)methanol:** $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.43-7.41(m, 2H), 7.20 (q, *J* = 7.8 Hz, 4H), 7.13 (d, *J* = 7.8 Hz, 2H), 5.70 (d, *J* = 3.0Hz, 1H), 2.38 (d, *J* = 3.6Hz, 1H), 2.32 (s, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 142.8, 140.5, 137.6, 131.4, 129.3, 128.1, 126.5, 121.2, 75.4, 21.1 ppm.



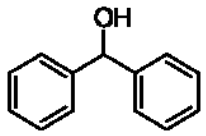

**(4-Bromophenyl)(4-methoxyphenyl)methanol:** $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.42 (d, *J* = 9.0 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 4H), 6.83 (d, *J* = 9.0 Hz, 2H), 3.76 (s, 3H), 2.49 (s, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 159.1, 142.9, 135.6, 131.4, 128.0, 127.8, 121.1, 113.9, 75.1, 55.2 ppm.



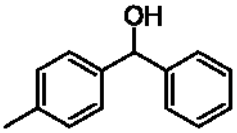

**(4-Bromophenyl)(*o*-tolyl)methanol:** $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.44-7.42(m, 3H), 7.22-7.15 (m, 5H), 5.93 (d, *J* = 3.0Hz, 1H), 2.23 (s, 3H), 2.22 (d, *J* = 3.6Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 141.8, 140.9, 135.3, 131.5, 130.7, 128.7, 127.8, 126.3, 126.2, 121.4, 72.7, 19.3 ppm.



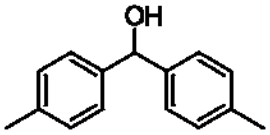

**(4-Chlorophenyl)( phenyl)methanol:** $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.33-7.28 (m, 4H), 7.27-7.24 (m, 5H), 5.74 (d, J=3.0Hz, 1H), 2.47 (d, J=3.0Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 143.4, 142.1, 133.2, 128.6, 128.5, 127.8, 127.8, 126.5, 75.5 ppm.



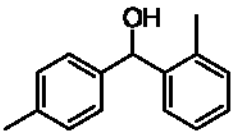
**Diphenylmethanol:** $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.34-7.29 (m, 8H), 7.25 - 7.23 (m, 2H), 5.77 (s, 1H), 2.39 (s, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 143.7, 128.4, 127.5, 126.5, 76.1 ppm.



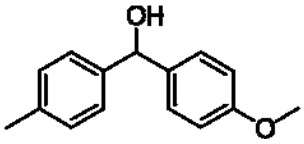
**Phenyl(*p*-tolyl)methanol:** $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.35 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.25 - 7.23 (m, 3H), 7.13 (d, *J* = 7.8 Hz, 2H), 5.77 (d, *J* = 3.6 Hz, 1H), 2.32 (s, 3H), 2.26 (d, *J* = 3.6 Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 143.9, 140.9, 137.2, 129.1, 128.4, 127.4, 126.5, 126.4, 76.0, 21.1 ppm.



**Di*p*-tolylmethanol:** $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.22 (d, *J* = 8.4 Hz, 4H), 7.11 (d, *J* = 8.4 Hz, 4H), 5.72 (d, *J* = 2.4 Hz, 1H), 2.31 (s, 6H), 2.29 (d, *J* = 3.6 Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 141.1, 137.2, 129.1, 126.4, 75.8, 21.0 ppm.

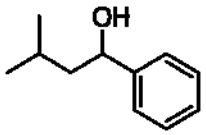


***o*-Tolyl(*p*-tolyl)methanol:** $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.51 (d, J = 9.6 Hz, 1H), 7.25 - 7.17 (m, 4H), 7.11-7.10 (m, 3H), 5.91 (s, 1H), 2.31 (s, 3H), 2.22 (s, 1H), 2.20 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 141.5, 139.9, 137.2, 135.2, 130.4, 129.1, 127.3, 127.0, 126.0, 73.1, 21.1, 19.3 ppm.

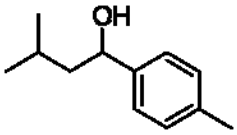


**(4-Methoxyphenyl)(*p*-tolyl)methanol:** $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.25 - 7.21 (m, 4H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.84-6.81 (m, 2H), 5.71 (d, *J* = 3.0 Hz, 1H), 3.75 (s, 3H), 2.36 (d, *J* = 3.6 Hz, 1H), 2.31

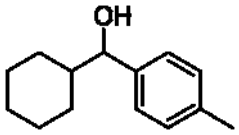
(s, 3H) ppm. $^{13}C$ NMR ($CDCl_3$, 150 MHz): δ 158.8, 141.1, 137.0, 136.3, 129.0, 127.7, 126.3, 113.7, 75.5, 55.2, 21.0 ppm.



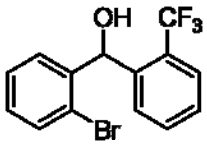

**3-Methyl-1-phenylbutan-1-ol:** $^{1}H$ NMR ($CDCl_3$, 600 MHz): δ 7.35-7.33 (m, 4H), 7.27-7.24 (m, 1H), 4.72 (t, J=7.2Hz, 1H), 1.97 (s, 1H), 1.74-1.67 (m, 2H), 0.95-0.93 (m, 6H) ppm. $^{13}C$ NMR ($CDCl_3$, 150 MHz): δ 145.2, 128.4, 127.4, 125.8, 72.7, 48.3, 24.8, 23.1, 22.2 ppm.




**3-Methyl-1-p-tolylbutan-1-ol:** $^{1}H$ NMR ($CDCl_3$, 600 MHz): δ 7.22 (d, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 4.68 (dt, *J* = 6.6, 2.4 Hz, 1H), 2.33 (s, 3H), 1.88 (br, 1H), 1.73-1.65 (m, 2H), 1.50-1.46 (m, 1H), 0.94-0.92 (m, 6H) ppm. $^{13}C$ NMR ($CDCl_3$, 150 MHz): δ 142.2, 137.1, 129.1, 125.8, 72.5, 48.2, 24.8, 23.0, 22.3, 21.1 ppm.

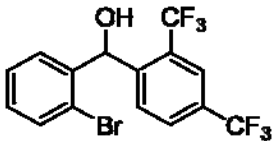



**Cyclohexyl(*p*-tolyl)methanol:** $^{1}H$ NMR ($CDCl_3$, 600 MHz): δ 7.14 (q, *J* = 7.8 Hz, 2H), 6.86 (d, *J* = 9.0Hz, 2H), 4.27 (d, *J* = 7.2Hz, 1H), 2.33 (s, 3H), 1.98-1.96 (m, 1H), 1.76-1.73 (m, 1H), 1.66-1.54 (m , 3H), 1.36-1.33 (m, 1H), 1.26-1.07 (m, 3H), 1.04-0.97 (m, 1H), 0.91-0.87 (m, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 150 MHz): δ 140.6, 136.9, 128.8, 126.5, 79.1, 44.8, 29.20, 28.9, 26.4, 26.0, 25.9, 21.0 ppm.

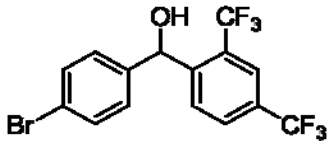



**(2-Bromophenyl)(2-(trifluoromethyl)phenyl)methanol:** White solid, m.p. 62-63$^{o}$C. $^{1}H$ NMR ($CDCl_3$, 600 MHz): δ 7.69 (d, *J* = 8.4

Hz,1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.42-7.39 (m, 3H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.16 (dt, *J* = 7.8 Hz,1.8Hz, 1H), 6.49 (d, *J* = 3.6 Hz, 1H) , 2.69 (d, *J* = 3.6 Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 141.3, 140.0, 133.1, 132.1, 129.3, 128.8, 128.7, 128.2 (q, *J* = 25.1 Hz), 128.0, 127.3, 126.3 (q, *J* = 5.1Hz), 123.6 (q, *J* = 227.3Hz), 123.0, 70.7 ppm. $^{19}$F NMR (282 MHz): δ -58.7 ppm. IR (neat, cm$^{-1}$): 3272(br), 2920(s), 1309(s), 1109(s), 1038(s). Anal. Calcd for $C_{14}H_{10}BrF_3O$: C, 50.78; H, 3.04; Found: C, 50.81; H, 2.88.

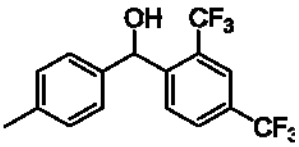



**(2,4-Bis(trifluoromethyl)phenyl)(2-bromophenyl)methanol:** White solid, m.p. 90-91°C. $^1$H NMR ($CDCl_3$, 600 MHz): δ 7.95 (s, 1H), 7.78 (d, *J* = 7.8 Hz,1H), 7.62 (d, *J* = 8.4 Hz,1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.33-7.29 (m, 2H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.54 (d, *J* = 4.2Hz, 1H) , 2.84 (d, *J* = 4.2 Hz, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 144.1, 140.5, 133.3, 130.5 (q, *J* = 27.9 Hz), 129.8, 129.1 (q, *J* = 26.5 Hz, 1C), 129.0, 128.5, 127.6, 123.6 (q, J = 1.9 Hz), 123.5 (q, *J* = 227.3 Hz), 123.3 (q, *J* = 227.3 Hz), 123.0, 70.4 ppm. $^{19}$F NMR (282 MHz): δ -58.1, -62.9 ppm. IR (neat, cm$^{-1}$): 3258(br), 1346(m), 1298(m), 1277(s), 1122(s). Anal. Calcd for $C_{15}H_9BrF_6O$: C, 45.14; H, 2.27; Found: C, 45.16; H, 2.16.




**(2,4-Bis(trifluoromethyl)phenyl)(4-bromophenyl)methanol:** Colorless oil. $^1$H NMR ($CDCl_3$, 600 MHz): δ 7.92 (s, 1H), 7.79 (q, *J* = 7.8 Hz, 2H), 7.46 (d, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 1H), 6.25 (s, 1H) , 2.69 (d, *J* = 3.6 Hz, 1H) ppm. $^{13}$CNMR ($CDCl_3$, 150 MHz): δ 145.7, 140.8, 131.7, 130.5 (q, *J* = 37.9 Hz), 130.3, 129.2, 128.3 (q,

*J* = 26.0 Hz), 128.1, 123.5 (q, *J* = 225.5 Hz), 123.2 (q, *J* = 225.5 Hz), 122.9 (q, *J* = 3.3 Hz), 122.1, 70.0 ppm. $^{19}$FNMR (282 MHz): δ -58.1, -62.9 ppm. IR (neat, $cm^{-1}$): 3315(br), 2928(s), 1345(m), 1300(m), 1275(s), 1124(s). Anal. Calcd for $C_{15}H_9BrF_6O$: C, 45.14; H, 2.27; Found: C, 45.43; H, 2.29.




**(2,4-Bis(trifluoromethyl)phenyl)(*p*-tolyl)methanol:** Colorless oil. $^1$H NMR ($CDCl_3$, 600 MHz): δ 7.91 (s, 2H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 8.4Hz, 2H), 7.15 (d, *J* = 8.4Hz, 2H), 6.30 (d, *J* = 2.4 Hz, 1H), 2.37 (d, *J* = 3.6 Hz, 1H), 2.33 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 146.4, 139.0, 137.9, 130.2, 130.1 (q, *J* = 27.9 Hz, 1C), 129.3, 129.0, 128.2 (q, *J* = 26.0 Hz), 126.4, 123.6 (q, *J* = 227.8 Hz), 123.3 (q, *J* = 227.8 Hz), 122.9 (q, *J* = 3.3 Hz), 70.6, 21.1 ppm. $^{19}$F NMR (282 MHz): δ -58.2, -62.9 ppm. IR (neat, $cm^{-1}$): 3341(br), 2959(s), 1346(m), 1301(m), 1275(s), 1126(s). HR-MS (-ESI): calcd. for $C_{17}H_{13}F_6O_3$ $[M+HCOO]^-$ 379.0778, found 379.0774.

**Reactions of palladacycle 3 with phenylboronic acid/phenylboroxine:** At room temperature, to a vial containing phenylboroxine (0.5 mmol), $K_3PO_4$ (ground, 0.25 mmol) and palladacycle **3** (0.000125 mmol) was added toluene (1 mL). 0.25 mmol of water was then immediately added into the reaction system by micro-syringe. The mixture was stirred and turned to black in less than 2 minutes.

To a vial containing phenylboroxine (0.5 mmol), $K_3PO_4$ (dried and ground, 0.25 mmol) and palladacycle **3** (0.000125 mmol) was added toluene (1 mL). The mixture was stirred

at room temperature and didn't turn to black after 2 hours.

**Reaction of palladacycle 3 with phenylmagnesium bromide:** To a vial containing palladacycle **3** (0.000125 mmol) was added toluene (1 mL). After palladacycle **3** was dissolved in toluene, PhMgBr (0.25 mmol, 0.25mL, 1M in THF) was injected. The mixture was stirred at room temperature and Pd balck was observed in less than 5 minutes.

**Palladacycle 3 catalyzed cross-coupling reactions of phenylboroxine with 2-bromotoulene or 2-bromoacetophenone:** To a vial containing 2-bromotoulene or 2-bromoacetophenone (0.25 mmol), arylboroxine (0.5 mmol), $K_3PO_4$ (dried and ground, 0.75 mmol) and palladacycle **3** (0.000125 mmol) was added toluene (1 mL). After the mixture was stirred at room temperature (about 20 $^oC$) for 6 hours, the reaction was quenched by adding a small amount of hydrochloric acid (2 N). The conversions, determined by GC-MS, were observed to be less 3%.

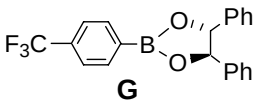
To a vial containing 2-bromotoulene or 2-bromoacetophenone (0.25 mmol), arylboroxine (0.5 mmol), $K_3PO_4$ (dried and ground, 0.75 mmol) and palladacycle **3** (0.000125 mmol) was added toluene (1 mL). 0.25mmol of water was then immediately added into the reaction system by micro-syringe. After the mixture was stirred at room temperature (about 20 $^oC$) for 6 hours, the reaction was quenched by adding a small amount of hydrochloric acid (2 N). The conversions, determined by GC-MS, were observed to be 73% for 2-bromotoulene and 50% for 2-bromoacetophenone, respectively.

**Palladacycle 3-catalyzed addition reactions of optically active *o*-tolylboronate with 2-bromo-benzaldehyde:** To a vial containing 2-bromobenzaldehyde (0.25 mmol), optically active boronate **E** (prepared by following Ref. 17) (0.5 mmol), $K_3PO_4$ (0.75 mmol) and palladacycle **3** (0.0025 mmol) was added toluene (1 ml). After the mixture was stirred at 0 $^oC$ for 80 hours, the reaction was quenched by adding small amount of water. Column chromatography on silica gel with ethyl acetate/hexane (v/v=1:10) afforded the alcohols. The analysis of enantiomerical excess was processed by HPLC with chiral OD column.

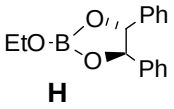
**(2-Bromophenyl)(2-methyl)methanol:** white solid. 45% yield, 5% e.e., [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 85:15, 1.0 ml/min, 230 nm UV detector]. $^1H$ NMR ($CDCl_3$, 600 MHz): δ 7.56 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8Hz, 1H), 7.29 (d, *J* = 6.0Hz, 2H), 7.23-7.14 (m, 4H), 6.28 (d, J = 4.2Hz, 1H), 2.29 (s, 3H), 2.26 (d, J = 4.8Hz, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 150 MHz): 141.8, 139.8, 136.0, 132.8, 130.5, 129.2, 128.8, 127.8, 127.6, 126.3, 126.1, 123.6, 72.1, 19.2 ppm.

**Experiments to exclude the possibility that optically active borates acted as Lewis acids:** To a vial containing 2-bromobenzaldehyde (0.25 mmol), phenylboroxine (0.125 mmol), optically active boronate **G** or borate **H** (0.125 mmol, prepared by following Ref. 18), $K_3PO_4$ (0.75 mmol) and palladacycle **3** (0.005 mmol) was added toluene (1 ml). After the mixture was stirred at 0 $^oC$ for 68 hours, the reaction was quenched by adding a small amount of water. Column chromatography on silica gel with ethyl acetate/hexane (v/v=1:10) afforded the alcohol products. The HPLC analysis showed no

enantioselectivity was observed for the addition reaction product.




**G**




**H**

**Palladacycle 3-catalyzed addition reactions of phenylboroxine or phenylborate with 3-phenylpropanal in the presence of optically active (*R,R*)-hydrobenzoin:** To a vial containing 2-bormobenzaldehyde (0.25 mmol), 2-methylphenylboroxine (0.125 mmol), (*R*,*R*)-1,2-diphenyl-1,2-ethanediol (0.25 mmol), $K_3PO_4$ (0.75 mmol) and palladacycle **3** (0.0025 mmol) was added toluene (1 mL). After the mixture was stirred at 0 $^oC$ for 60 hours, the reaction was quenched by adding a small amount of water. Column chromatography on silica gel with ethyl acetate/hexane (v/v=1:10) afforded the alcohol products. The HPLC analysis showed no enantioselectivity was observed for the addition reaction product.

# Chapter 3. CuCl/Bipyridine-Catalyzed Addition Reactions of Arylboroxines with Aldehydes, α,β-Unsaturated Ketones and *N*-Tosyl Aldimines

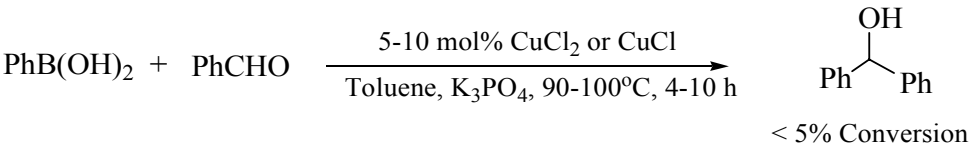
## 3.1 Introduction

Although enormous success for transition metal-catalyzed addition reactions of organoboron reagents with carbonyl-containing compounds and imines, including promising enantioselectivity, has been achieved,[6-14,14c,14d] most of the transition metal catalysts are expensive and/or require air-free handling operation. The search for operationally convenient and cost-effective catalysts for this type of addition reactions continues.

In our laboratory, we're interested in employing readily available transition metal complexes as catalysts for this type of addition reaction. In previous chapters, we described air/moisture-stable anionic four-electron donor-based (Type I) metalacycles,[11] a large family of cyclic organometallic compounds, as catalysts for such addition reactions.[12, 13] Other members from our group also reported $[Rh(COD)Cl]_2$ and $Ni(COD)_2$/4-$RCOC_6H_4Cl$-catalyzed addition reactions of arylborons with aldehydes[2a, 4a]. We have been interested in using Cu complexes as catalysts for this type of addition reactions because Cu(I) or Cu(II) salts such as CuCl or $CuCl_2$ are inexpensive. So far, some groups have studied such addition reaction with Cu catalysts. Shibasaki and Kanai reported $CuF_2$ (10 mol %)/(*R*)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)-phosphino] -4,4′-bi-1,3-benzo-dioxole(20 mol %) with tetrabutylammonium difluorotriphenyl silicate (TBAT, 15 mol%) as additive for the addition reaction of arylborates with aldehydes.[5b] Wu and Ding reported the use of Cu(II) acetate/dppf complex as catalyst for such

addition reaction of arylboronic acids with reactive aldehydes.[5a] Very recently, Ohmiya and Sawamura documented CuCl/1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene-catalyed 1,4-addition reactions of alkylboranes with imidazolyl α,β-unsaturated ketones.[35] Shintani and Hayashi described a 1,4-addition of arylboronic acid esters to alkylidene cyanoacetates catalyzed by a copper/*N*-heterocyclic carbene complex.[36] While these protocols are useful, there are drawbacks associated with them, *e.g.*, the requirement of additives and/or a very limited substrate scope. In our early study, we also found low conversions (< 5%) were observed for the addition reaction of phenylboronic acid with benzaldehyde, presumably because of the decomposition of the catalyst under the reaction condition.

**Scheme 3.1** $CuCl_2$ or CuCl-Catalyzed Addition Reaction of Phenylboronic Acid with Benzaldehyde



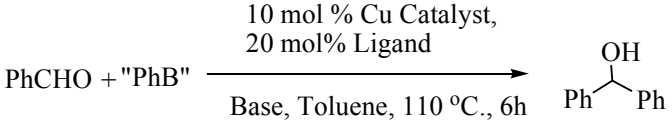

< 5% Conversion

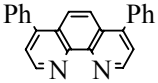
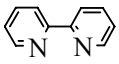
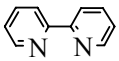
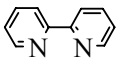
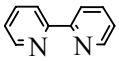
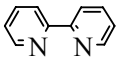
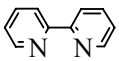
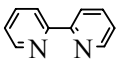
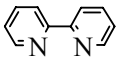
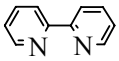
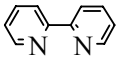
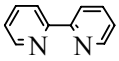
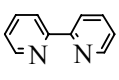
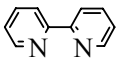
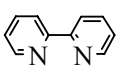
As described in Chapter 2, we demonstrated that palladacycle **3**-catalyzed addition reactions can efficiently occur under an anhydrous condition via non-transmetalation pathway and the palladacycle catalysts were found to be very stable under such anhydrous condition.[14] We thus surmised that Cu(I)/(II) catalysts might also be long-lived under the anhydrous condition and might be able to function as efficient catalysts for the addition reactions. In this chapter, we report our study on such addition reactions with simple Cu(I)/(II) complexes, specifically, CuCl/bipyridine-catalyzed addition reactions of arylboroxines with aldehydes, α,β-unsaturated ketones and *N*-tosyl aldimines.

## 3.2 Exploring the Reaction Condition of Copper-Catalyzed Addition Reactions of Arylborons with aldehydes

Our study began with the testing of several copper complexes as catalysts for the addition reaction of phenylboronic acid with benzaldehyde under the anhydrous condition. By using dry $K_3PO_4$, toluene and dry phenylboronic acid (phenylboroxine), we found that although a low efficiency was observed by using $CuCl_2$, CuCl, $CuCl_2$/dppf, $CuCl_2$/4,7-diphenyl-1,10-phenanthroline, $CuCl_2$/tetramethylethane-1,2-diamine, or $CuCl_2$/pyridine complex (Table 3.1, entries 1-6), $CuCl_2$/bipyridine exhibited a promising catalytic activity (Table 3.1, entry 7). Further study revealed that CuCl/bipyridine was the most active complexes and NaOAc was the best base (Table 3.1, entries 7-15). The catalytic system showed a higher activity at higher temperature with *o*-xylene as the solvent (Table 3.1, entry 16). We also examined other phenylboron reagents and found that only phenylboroxine showed reactivity (Table 3.1, entries 17-20).

**Table 3.1** Copper-catalyzed 1,2-Addition Reaction of Phenylboron Reagents with Benzaldehyde [a]




| entry | catalyst | ligand | "PhB" | base | conv.(%)[b] |
|---|---|---|---|---|---|
| 1 | $CuCl_2$ | - | $(PhBO)_3$ | $K_3PO_4$ | <1 |
| 2 | CuCl | - | $(PhBO)_3$ | $K_3PO_4$ | <1 |
| 3 | $CuCl_2$ | DPPF | $(PhBO)_3$ | $K_3PO_4$ | 7 |
| 4 | $CuCl_2$ |  | $(PhBO)_3$ | $K_3PO_4$ | 7 |
| 5 | $CuCl_2$ |  | $(PhBO)_3$ | $K_3PO_4$ | 3 |
| 6 | $CuCl_2$ |  | $(PhBO)_3$ | $K_3PO_4$ | <1 |
| 7 | $CuCl_2$ |  | $(PhBO)_3$ | $K_3PO_4$ | 25 |
| 8 | $CuCl_2$ |  | $(PhBO)_3$ | $K_2CO_3$ | 18 |
| 9 | $CuCl_2$ |  | $(PhBO)_3$ | $Cs_2CO_3$ | 8 |
| 10 | $CuCl_2$ |  | $(PhBO)_3$ | KOAc | 59 |
| 11 | $CuCl_2$ |  | $(PhBO)_3$ | NaOAc | 66 |
| 12 | $CuCl_2$ |  | $(PhBO)_3$ | KF | 67 |
| 13 | CuCl |  | $(PhBO)_3$ | NaOAc | 78 |
| 14 | CuCl |  | $(PhBO)_3$ | KF | 63 |
| 15 | $Cu(OAc)_2$ |  | $(PhBO)_3$ | NaOAc | 40 |
| 16 | CuCl |  | $(PhBO)_3$ | NaOAc | 96 [c] |
| 17 | CuCl |  | $PhB(OH)_2$ | NaOAc | <1 |
| 18 | CuCl |  |  | NaOAc | <1 |
| 19 | CuCl |  |  | NaOAc | <1 |
| 20 | CuCl |  | $PhBF_3K$ | NaOAc | <1 |

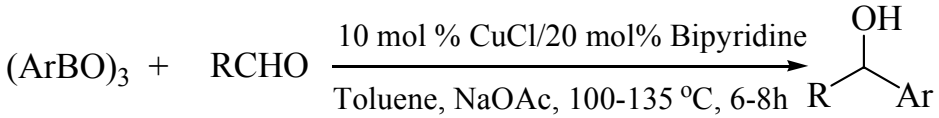
a. Reaction conditions: Benzaldehyde (0.25 mmol), phenylboron reagent (2.0 equiv), Base (3.0 equiv), 10% of Cu catalyst, 20% of ligand, 110 °C, 8 h. b. NMR result. c. *o*-Xylene was used as solvent at 135 °C.

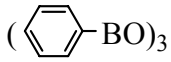
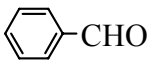
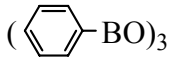
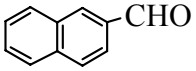
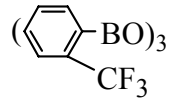
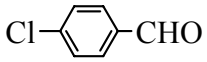
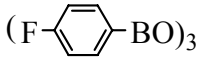
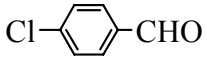
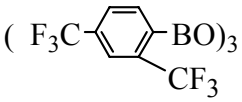
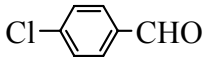
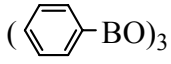
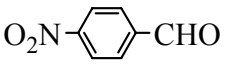
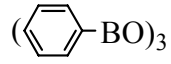
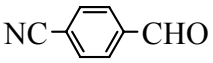
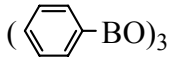
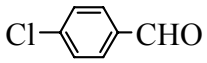
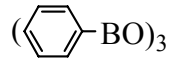
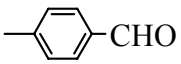
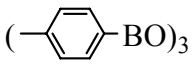
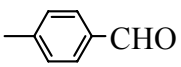
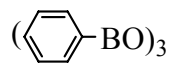
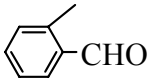
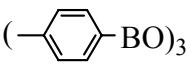
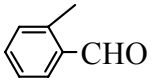
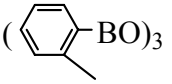
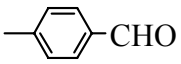
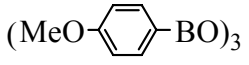
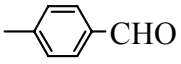
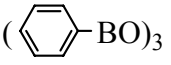
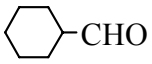
### 3.3 Reaction Scope of CuCl/Bipyridine-Catalyzed Addition Reactions of Arylboroxines with Aldehydes, α, β-Unsaturated Ketones and *N*-Tosyl Aldimines

With 10 mol% CuCl/20 mol % bipyridine as the catalyst, NaOAc as the base and *o*-xylene as solvent, different arylboroxines and aldehydes for the addition reactions were examined and our results are listed in Table 3.2. The addition reactions with the aldehydes bearing neutral or electron-withdrawing groups proceeded smoothly with arylboroxines bearing electron-donating and electron-withdrawing groups. The corresponding diarylmethanols were obtained in good yields (Method A, Table 3.2, entry 1-5). The phenylboroxine can react with more reactive electron-withdrawing aldehydes smoothly at a lower temperature (Method B, Table 3.2, entry 6-8). Less reactive, electron-donating group-containing aldehydes and aliphatic aldehyde can react with various arylboroxines in moderate to good yields by simply increasing the catalyst loading to 20 mol % of CuCl/ 40 mol % of bipyridine (Method C, Table 3.2, entry 9-15).

Recently, our group reported Pd(II), Pt(II), Rh(I)-catalyzed addition reactions of arylboronic acids with alkyl 2-formylbenzoates followed by lactonization to access 3-substituted phthalides.[37] Since CuCl/bipyridine can catalyze addition reaction of aldehydes with arylboroxines efficiently, we envisioned that such catalyst system might also catalyze the addition reactions of arylboroxines with methyl 2-formylbenzoates to access 3-substituted phthalides. Our experiments showed that 3-substituted phthalides were obtained in good to excellent yields (Table 3.3).

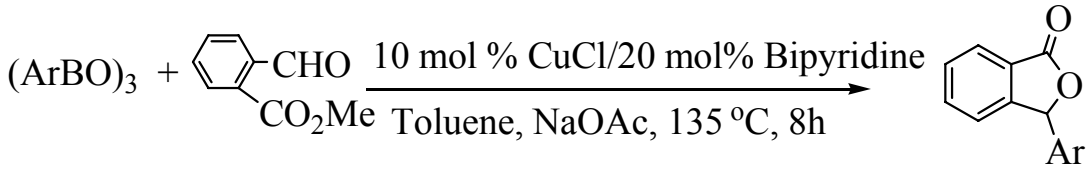
**Table 3.2** CuCl/Bipyridine-Catalyzed Addition Reactions of Arylboroxines with Aldehydes [a]

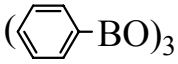
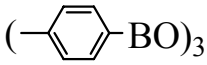
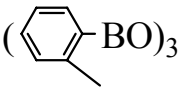
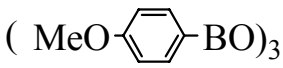



| Entry | $(ArBO)_3$ | RCHO | Condition | Yield(%)[b] |
|---|---|---|---|---|
| 1 |  |  | **A** | 86 |
| 2 |  |  | **A** | 85 |
| 3 |  |  | **A** | 83 |
| 4 |  |  | **A** | 85 |
| 5 |  |  | **A** | 86 |
| 6 |  |  | **B** | 87 |
| 7 |  |  | **B** | 85 |
| 8 |  |  | **B** | 88 |
| 9 |  |  | **C** | 87 |
| 10 |  |  | **C** | 83 |
| 11 |  |  | **C** | 80 |
| 12 |  |  | **C** | 83 |
| 13 |  |  | **C** | 88 |
| 14 |  |  | **C** | 81 |
| 15 |  |  | **C** | 62 |

a. Reaction conditions: aldehydes (1.0 equiv), arylboronic acid (2.0 eq), A: 10 mol % CuCl, 20 mol% bipyridine, *o*-xylene, 135 °C, 6 h; B: 10 mol % CuCl, 20 mol% bipyridine, toluene, 110 °C, 6 h; C: 20 mol % CuCl, 40 mol% bipyridine, *o*-xylene, 135 °C, 6 h;b. Isolated yields.

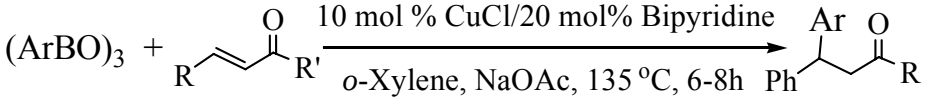
**Table 3.3** CuCl/Bipyridine-Catalyzed Addition Reactions of Arylboroxines with Methyl-2-formylbenzoate [a]

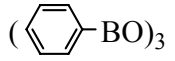
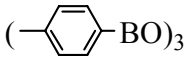
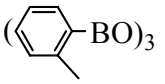
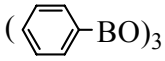
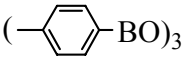
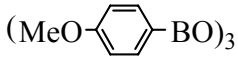
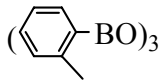
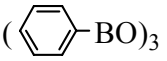
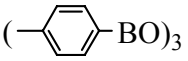



| Entry | $(ArBO)_3$ | Yield(%)[b] |
|---|---|---|
| 1 |  | 92 |
| 2 |  | 83 |
| 3 |  | 81 |
| 4 |  | 80 |

In addition, we found that CuCl/bipyridine was also an efficient catalyst for 1,4-addition reaction of arylboroxines with α,β-unsaturated ketones (Table 3.4). Complete conversions and high yields were obtained for all tested substrates. To our knowledge, this represents the first example of Cu-catalyzed 1,4-addition reaction of arylboron reagents with α,β-unsaturated ketones.

**Table 3.4** CuCl/Bipyridine-Catalyzed Addition Reactions of Arylboroxines with α,β-Unsaturated Ketones [a]



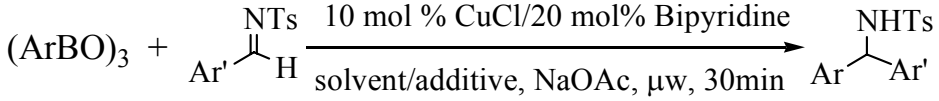

| Entry | $(ArBO)_3$ | R | R' | Yield(%)[b] |
|---|---|---|---|---|
| 1 |  | Ph | Ph | 89 |
| 2 |  | Ph | Ph | 82 |
| 3 |  | Ph | Ph | 80 |
| 4 |  | Ph | $CH_3$ | 85 |
| 5 |  | Ph | $CH_3$ | 83 |
| 6 |  | Ph | $CH_3$ | 82 |
| 7 |  | Ph | $CH_3$ | 81 |
| 8 |  | *n*-$C_4H_9$ | $CH_3$ | 85 |
| 9 |  | *n*-$C_4H_9$ | $CH_3$ | 84 |

a. Reaction conditions: aldehydes (1.0 equiv), arylboronic acid (2.0 eq), A: 10 mol % CuCl, 20 mol% bipyridine, *o*-xylene, 135 °C, 6 h; b. Isolated yields.

We also examined the addition reaction of arylboroxines with *N*-tosyl aldimine. We found that CuCl/bipyridine complex can efficiently catalyze the addition reaction of arylboroxines with *N*-tosyl aldimine with toluene and 4-chlorotoluene as co-solvents and generate up to 84% conversion (Table 3.5, entry 1-3), which is promising. The complete conversions and moderate yields can be achieved under assistance of microwave energy (Table 3.5, entry 4-9). Since we found that all the starting material, *N*-tosyl aldimines have disappeared, only moderate yields achievement suggested that some aldimines decomposed through the reaction under such conditions. To our knowledge, this

represents the first example of Cu complex-catalyzed addition reaction of organoborons with aldimines.

**Table 3.5** Microwave-Assisted, CuCl/Bipyridine-Catalyzed Addition Reactions of Arylboroxines with *N*-Tosyl Aldimine [a]




| Entry | Ar | Ar' | Solvent | Temp.(°C) | Yield(%)[b] |
|---|---|---|---|---|---|
| 1 | Ph | Ph | Toluene | 110[c] | 50[d] |
| 2 | Ph | Ph | *o*-Xylene | 135[c] | 52[d] |
| 3 | Ph | Ph | Toluene/ 4-chlorotulene | 135[c] | 84[d] |
| 4 | Ph | Ph | Toluene/ 4-chlorotulene | 180 | 70 |
| 5 | 4-$CH_3C_6H_4$ | Ph | Toluene/ 4-chlorotulene | 180 | 61 |
| 6 | 2-$CH_3C_6H_4$ | Ph | Toluene/ 4-chlorotulene | 180 | 65 |
| 7 | 4-$CH_3OC_6H_4$ | Ph | Toluene/ 4-chlorotulene | 180 | 62 |
| 8 | Ph | 4-$CH_3C_6H_4$ | Toluene/ 4-chlorotulene | 180 | 58 |
| 9 | Ph | 4-$ClC_6H_4$ | Toluene/ 4-chlorotulene | 180 | 69 |

[a]Reaction conditions: aldehydes (1.0 equiv), arylboronic acid (2.0 eq), 10 mol % CuCl, 20 mol% bipyridine,NaOAc(3.0 equiv), 135 °C for 6 h or 180°C for 30 min; [b]Isolated yields. [c]Conventional heating by oil bath for 6 hours.[d]Conversion base on $^1$H NMR

In summary, we demonstrated that inexpensive CuCl/bipyridine complex was an active catalyst for addition reactions of arylboroxines with aldehydes, alkyl 2-formylbenzoates, enones and *N*-tosyl aldimine. Our future work will directly be focus on the elucidation of detailed reaction mechanism and applying the reaction in organic synthesis.

### 3.4 Experimental Section

**General.** NMR spectra were recorded on 300 or 600 MHz spectrometers (300 or 600 MHz for $^{1}$H NMR, 150 MHz for $^{13}$C NMR and 287MHz for $^{19}$F NMR) with $CDCl_3$ as the solvent.

**General procedure for CuCl/Bipyridine-Catalyzed Addition Reactions of Arylboroxines with Aldehydes:** In a dry-box, to a vial containing aldehyde (0.25 mmol), arylboroxines (0.5 mmol), base (NaOAc, 0.75 mmol) and CuCl/Bipyridine (Condition A, B or D: 0.025 mmol/0.05 mmol; Condition C: 0.05 mmol/0.1mmol) were added solvent (1.0 mL, Condition A, C or D: *o*-xylene; Condition B: toluene). After the mixture was stirred out of drybox at 110 $^{o}$C (Condition B) or 135$^{o}$C (Condition A, C or D) for 6-8 hours, the reaction was quenched by adding 4 N HCl (2 mL) aqueous solution. The mixture was extracted with $CH_2Cl_2$ (3 x15 mL). The organic layers were combined. After evaporation of the organic solvents, the residue was subjected to column chromatography [silica gel, ethyl acetate/hexane (v/v=1:10) as eluent] to afford the products.

**Phenyl(*p*-tolyl)methanol:** $^{1}$H NMR δ 7.34 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.24 - 7.22 (m, 3H), 7.12 (d, *J* = 7.8 Hz, 2H), 5.75 (s, 1H), 2.36 (br, 1H), 2.31 (s, 3H). $^{13}$C NMR δ 143.9, 140.9, 137.2, 129.1, 128.4, 127.4, 126.5, 126.4, 76.0, 21.1.

**Di*p*-tolylmethanol:** $^{1}$H NMR δ 7.22 (d, *J* = 7.2 Hz, 4H), 7.11 (d, *J* = 7.8 Hz, 4H), 5.72 (s, 1H), 2.31 (s, 6H), 2.27 (s, 1H). $^{13}$C NMR δ 141.1, 137.0, 129.1, 126.4, 75.8, 21.0.

***o*-Tolyl(*p*-tolyl)methanol:** $^{1}$H NMR δ 7.51 (d, J = 7.2 Hz, 1H), 7.25 - 7.17 (m, 3H), 7.11-7.10 (m, 4H), 5.91 (s, 1H), 2.31 (s, 3H), 2.22 (s, 1H), 2.20 (s, 3H). $^{13}$C NMR δ 141.5, 139.9, 137.2, 135.2, 130.4, 129.1, 127.3, 127.0, 126.0, 73.1, 21.1, 19.3.

**(4-Methoxyphenyl)(*p*-tolyl)methanol:** $^{1}$H NMR δ 7.24 (d, *J* = 9.0 Hz, 2H), 7.22 (d, *J* =

8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 5.72 (s, 1H), 3.75 (s, 3H), 2.31 (s, 4H). $^{13}$C NMR δ 158.9, 141.1, 137.0, 136.3, 129.0, 127.7, 126.3, 113.7, 75.5, 55.2, 21.0.

**Phenyl(*o*-tolyl)methanol:** $^{1}$H NMR δ 7.50 (d, *J* = 7.8 Hz, 1H), 7.31-7.30 (4 m, H), 7.27-7.22 (m, 2H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 5.98 (d, *J* = 3.6 Hz, 1H), 2.23 (s, 3H), 2.17 (d, *J* = 4.2 Hz, 1H). $^{13}$C NMR δ 142.8, 141.4, 135.3, 130.5, 128.4, 127.5(2C), 127.1, 126.2, 126.1, 73.3, 19.4.

**Diphenylmethanol:** $^{1}$H NMR δ 7.33-7.28 (m, 8H), 7.23 (t, *J* = 7.2 Hz, 2H), 5.74 (s, 1H), 2.45 (s, 1H). $^{13}$C NMR δ 143.7, 128.4, 127.5, 126.5, 76.1.

**Naphthalen-2-yl(phenyl)methanol:** $^{1}$H NMR δ 7.80 (s, 1H), 7.77-7.75 (m, 2H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.44-7.41 (m, 2H), 7.36-7.33 (m, 3H), 7.27 (t, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 5.86 (d, *J* = 3.0 Hz, 1H), 2.61 (s, 1H). $^{13}$C NMR δ 143.5, 141.0, 133.2, 132.8, 128.4, 128.2, 128.0, 127.6, 127.5, 126.6, 126.1, 125.9, 124.9, 124.7, 76.2.

**4-(Hydroxy(phenyl)methyl)benzonitrile:** $^{1}$H NMR δ 7.58 (d, *J* = 8.4 Hz, 2H), 7.48 (t, *J* = 8.4 Hz, 2H), 7.35 -7.28 (m, 5H), 5.75 (d, *J* = 3.0 Hz, 1H), 2.70 (d, *J* = 3.6 Hz, 1H). $^{13}$C NMR δ 148.8, 142.7, 132.2, 128.8, 128.2, 126.9, 126.6, 118.8, 110.9, 75.5.

**(4-Chlorophenyl)(phenyl)methanol:** $^{1}$H NMR δ 7.33 -7.30 (m, 4H), 7.28 -7.25 (m, 5H), 5.74 (d, *J* = 2.4 Hz, 1H), 2.49 (d, *J* = 2.4 Hz, 1H). $^{13}$C NMR δ 143.3, 142.1, 133.2, 128.6, 128.5, 127.8, 127.7, 126.5, 75.5.

**(4-Nitrophenyl)(phenyl)methanol:** $^{1}$H NMR δ 8.19 (d, *J* = 7.2 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.38 -7.30 (m, 5H), 5.92 (d, *J* = 3.0 Hz, 1H), 2.40 (d, *J* = 3.0 Hz, 1H). $^{13}$C NMR δ 150.7, 147.2, 142.7, 129.0, 128.4, 127.0, 126.7, 123.7, 75.5.

**(4-Chlorophenyl)(2-(trifluoromethyl)phenyl)methanol:** $^{1}$H NMR δ 7.67 (d, *J* = 8.4

Hz,1H), 7.57 -7.52 (m, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.28 (s, 4H), 6.25 (s, 1H) , 2.46 (d, *J* = 3.6 Hz, 1H). $^{13}$C NMR δ 141.9, 141.2, 133.3, 132.4, 129.4, 128.5, 128.0, 127.8, 127.6 (q, *J* = 29.7 Hz), 125.6 (q, *J* = 5.6Hz), 124.3 (q, *J* = 272.3Hz), 70.7 (q, *J* = 2.3Hz).

**(2,4-Bis(trifluoromethyl)phenyl)(4-chlorophenyl)methanol:** Light yellow oil. $^{1}$H NMR δ 7.92 (s, 1H), 7.81-7.77 (m, 2H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 6.27 (s, 1H) , 2.67 (d, *J* = 3.6 Hz, 1H) ppm. $^{13}$C NMR δ 145.8, 140.3, 133.9, 130.5 (q, *J* = 33.5 Hz, 1C), 130.3, 129.2, 128.8, 128.3 (q, *J* = 30.6 Hz), 127.8, 123.5 (q, *J* = 272.7 Hz), 123.2 (q, *J* = 272.7 Hz), 123.0 (q, *J* = 3.9 Hz), 70.0. $^{19}$F NMR: δ -58.9, -63.7 ppm. IR: 3325(br), 1491(s), 1345(m), 1300(s), 1124(s). HR-MS (-ESI): calcd. for $C_{16}H_{10}ClF_6O_3$ $[M+HCOO]^-$ 399.0228, found 399.0231.

**(4-Chlorophenyl)(4-fluorophenyl)methanol:** $^{1}$H NMR δ 7.30-7.25 (m, 6H), 7.01 (t, *J* = 9.0 Hz, 2H), 5.75 (s, 1H), 2.42 (d, *J* = 2.4 Hz, 1H). $^{13}$C NMR δ 162.3 (d, *J* = 245.4 Hz), 142.0, 139.2 (d, *J* = 2.9 Hz), 133.4, 128.7, 128.2 (d, *J* = 7.8 Hz), 127.8, 115.5 (d, *J* = 21.2 Hz), 74.9.

**Cyclohexyl(phenyl)methanol:** $^{1}$H NMR δ 7.32 (t, *J* = 7.2 Hz, 2H), 7.28-7.24 (m, 3H), 4.27 (dd, *J* = 3.0, 7.2Hz, 1H), 1.98-1.96 (m, 1H), 1.93 (d, *J* = 3.0 Hz, 2H), 1.77-1.74 (m, 1H), 1.66-1.57 (m, 3H), 1.37-1.35 (m, 1H), 1.25-1.00 (m, 4H), 0.95-0.89 (m, 1H). $^{13}$C NMR δ 143.6, 128.1, 127.3, 126.6, 79.3, 44.9, 29.2, 28.8, 26.4, 26.0, 25.9.

**3-Phenylisobenzofuran-1(3H)-one:** $^{1}$H NMR δ 7.95 (d, *J* = 7.2 Hz, 1H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.55 (t, *J*=7.8 Hz, 1H), 7.38-7.26 (m, 6H), 6.40 (s, 1H). $^{13}$C NMR δ 170.5, 149.6, 136.3, 134.3, 129.3, 129.2, 128.9, 126.9, 125.5, 125.5, 122.8, 82.6.

**3-*p*-Tolylisobenzofuran-1(3H)-one** $^{1}$H NMR δ 7.95 (d, *J*=8.4 Hz, 1H), 7.63 (t, *J*=7.8 Hz, 1H), 7.54 (t, *J*=7.8 Hz, 1H), 7.32 (t, *J*=7.8 Hz, 1H), 7.18-7.14 (m, 4H), 6.37 (s, 1H), 2.34

(s, 3H). $^{13}$C NMR δ 170.5, 149.7, 139.2, 134.2, 133.3, 129.5, 129.2, 127.0, 125.6, 125.5, 122.8, 21.1.

**3-*o*-Tolylisobenzofuran-1(3H)-one:** $^{1}$H NMR δ 7.97 (d, *J*=7.8 Hz, 1H), 7.66 (t, *J*=7.2 Hz, 1H), 7.56 (t, *J*=7.2 Hz, 1H), 7.33 (d, *J*=7.8 Hz, 1H), 7.28-7.24 (m, 2H), 7.12 (t, *J*=7.8 Hz, 1H), 6.91 (d, *J*=7.8 Hz, 1H), 6.67 (s, 1H), 2.49 (s, 3H). $^{13}$C NMR δ 170.5, 149.2, 137.1, 134.1, 134.0, 131.0, 129.3, 129.2, 127.1, 126.3, 126.3, 125.6, 123.0, 80.4, 19.2.

**3-(4-Methoxyphenyl)isobenzofuran-1(3H)-one:** $^{1}$H NMR δ 7.95 (d, *J*=7.8 Hz, 1H), 7.64 (t, *J*=7.2 Hz, 1H), 7.55 (t, *J*=7.2 Hz, 1H), 7.31 (d, *J*=7.8 Hz, 1H), 7.17 (d, *J*=7.8 Hz, 1H), 6.88 (d, *J*=8.4 Hz, 1H), 6.37 (s, 1H), 3.80 (s, 3H). $^{13}$C NMR δ 170.5, 163.4, 149.7, 134.2, 129.3, 128.8, 128.3, 125.9, 125.5, 122.9, 114.3, 82.7, 55.3, 21.1.

**General procedure for CuCl/Bipyridine-Catalyzed Addition Reactions of Arylboroxines with α,β-Unsaturated Ketones:** In a dry-box, to a vial containing α,β-Unsaturated Ketones (0.25 mmol), arylboroxines (0.5 mmol), base (NaOAc, 0.75 mmol) and CuCl/Bipyridine (0.025 mmol/0.05 mmol) were added *o*-xylene (1.0 mL). After the mixture was stirred out of drybox at 135$^{o}$C for 6-8 hours, the reaction was quenched by adding 4 N HCl (2 mL) aqueous solution. The mixture was extracted with $CH_2Cl_2$ (3 x15 mL). The organic layers were combined. After evaporation of the organic solvents, the residue was subjected to column chromatography [silica gel, ethyl acetate/hexane (v/v=1:20) as eluent] to afford the products.

**1,3,3-Triphenylpropan-1-one:** $^{1}$H NMR δ 7.92 (d, *J* = 6.6 Hz, 2H), 7.51 (t, *J* = 6.6 Hz, 1H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.26-7.25 (m, 8H), 7.17-7.14 (m, 2H), 4.83 (t, *J* = 7.2Hz, 1H), 3.72 (d, *J* = 7.2Hz, 2H). $^{13}$C NMR δ 197.9, 144.1, 137.0, 133.0, 128.5, 128.4, 128.0, 127.8, 126.3, 45.9, 44.7.

**1,3-Diphenyl-3-*p*-tolylpropan-1-one:** $^{1}$H NMR δ 7.93 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 6.6 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.26 (t, *J* = 4.8 Hz, 2H), 7.17-7.15 (m, 3H), 7.07 (d, *J* = 7.8 Hz, 2H), 4.79 (t, *J* = 7.2Hz, 1H), 3.72 (d, *J* = 7.8Hz, 2H), 2.28 (s, 3H). $^{13}$C NMR δ 198.0, 144.4, 141.1, 137.1, 135.9, 133.0, 129.2, 128.6, 128.5, 128.0, 127.8, 127.6, 126.3, 45.5, 44.8, 21.0.

**1,3-Diphenyl-3-*o*-tolylpropan-1-one:** $^{1}$H NMR δ 7.92 (d, *J* = 7.8 Hz, 2H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.25 (t, *J* = 8.4 Hz, 2H), 7.23-7.20 (m, 3H), 7.17-7.09 (m, 4H), 5.02 (t, *J* = 7.2 Hz, 1H), 3.71 (m, 2H), 2.32 (s, 3H). $^{13}$C NMR δ 198.0, 143.7, 141.8, 137.0, 136.4, 133.0, 130.7, 128.6, 128.4, 128.0, 127.9, 126.3, 126.2, 126.0, 45.0, 41.8, 19.9.

**4,4-Diphenylbutan-2-one:** $^{1}$H NMR δ 7.27 (t, *J* = 7.8 Hz, 4H), 7.24 (d, *J* = 7.2 Hz, 4H), 7.17 (t, *J* = 7.2 Hz, 2H), 4.59 (t, *J* = 7.2Hz, 1H), 3.18 (d, *J* = 7.8 Hz, 2H), 2.08 (s, 3H). $^{13}$C NMR δ 206.9, 143.8, 128.6, 127.7, 126.4, 49.7, 46.0, 30.6.

**4-Phenyl-4-*p*-tolylbutan-2-one:** $^{1}$H NMR δ 7.25 (t, *J* = 7.2 Hz, 2H), 7.21 (d, *J* = 7.2 Hz, 2H), 7.16 (t, *J*=7.2 Hz, 1H), 7.11-7.07 (m, 4H), 4.54 (t, *J*=7.2 Hz, 1H), 3.15 (d, *J*=7.2 Hz, 2H), 2.28 (s, 3H), 2.06 (s, 3H). $^{13}$C NMR δ 206.9, 144.0 140.7, 135.9, 129.2, 128.5, 127.5, 127.4, 126.3, 49.7, 45.6, 30.6, 20.9.

**4-Phenyl-4-*o*-tolylbutan-2-one:** $^{1}$H NMR δ 7.25-7.22 (m, 3H), 7.19-7.09 (m, 6H), 4.78 (t, *J*=7.2 Hz, 1H), 3.14 (d, *J*=7.2 Hz, 2H), 2.29 (s, 3H), 2.06 (s, 3H). $^{13}$C NMR δ 206.9, 143.4, 141.5, 136.3, 130.7, 128.4, 127.9, 126.40, 126.2 (2C), 126.0, 50.0, 41.9, 30.6, 19.8.

**4-(4-Methoxyphenyl)-4-phenylbutan-2-one:** $^{1}$H NMR δ 7.26 (t, *J*=7.2 Hz, 4H), 7.21-7.19 (m, 2H), 7.16 (t, *J*=7.2 Hz, 2H), 7.13 (d, *J*=7.2 Hz, 2H ), 6.81 (d, *J*=7.2 Hz, 2H),

4.53 (t, *J*=7.2 Hz, 1H), 3.75 (s, 3H,), 3.14 (d, *J*=7.8 Hz, 2H), 2.06 (s, 3H). $^{13}$C NMR δ 207.0, 158.0, 144.2, 135.9, 128.6, 128.5, 127.5, 126.3, 113.9, 55.1, 49.8, 45.2, 30.6.

**4-Phenyloctan-2-one:** $^{1}$H NMR δ 7.28 (t, *J*=7.8 Hz, 2H), 7.20-7.16 (m, 3H), 3.10 (m, 1H), 2.75-2.67 (m, 2H), 2.01 (s, 3H), 1.65-1.52 (m, 2H), 1.31-1.18 (m, 2H), 1.17-1.05 (m, 2H), 0.82 (t, *J*=7.2 Hz, 3H). $^{13}$C NMR δ 208.0, 144.6, 128.4, 127.4, 126.3, 50.9, 41.3, 36.2, 30.6, 29.5, 25.6, 22.6, 13.9.

**4-*p*-Tolyloctan-2-one:** $^{1}$H NMR δ 7.09 (d, *J*=8.4 Hz, 2H), 7.05 (d, *J*=7.8 Hz, 2H), 3.07-3.05 (m, 1H), 2.72-2.67 (m, 2H), 2.30 (s, 3H), 2.00 (s, 3H), 1.61-1.51 (m, 2H), 1.28-1.20 (m, 2H), 1.16-1.07 (m, 2H), 0.82 (t, *J*=7.2 Hz, 3H). $^{13}$C NMR δ 208.2, 141.5, 135.7, 129.1, 127.3, 51.1, 40.9, 36.2, 30.6, 29.6, 22.6, 21.0, 13.9.

**General procedure for CuCl/Bipyridine-Catalyzed Addition Reactions of Arylboroxines with *N*-Tosyl Aldimine:** In a dry-box, to a 10-ml pressure vial containing *N*-Tosyl Aldimine (0.25 mmol), arylboroxines (0.5 mmol), base (NaOAC, 0.75 mmol) and CuCl/Bipyridine (0.025 mmol/0.05 mmol) were added toluene/4-chlorotoluene (total 1.0 mL, 1:1 ratio). After the mixture was irradiated by microwave at 180 $^{o}$C for 30 minutes, the reaction was quenched by adding 4 N HCl (2 mL) aqueous solution. The mixture was extracted with $CH_2Cl_2$ (3 x15 mL). The organic layers were combined. After evaporation of the organic solvents, the residue was subjected to column chromatography [silica gel, ethyl acetate/hexane (v/v=1:20) as eluent] to afford the products.

***N*-Benzhydryl-4-methylbenzenesulfonamide:** $^{1}$H NMR δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.21-7.09 (m, 12H), 5.57 (d, *J* = 7.8 Hz, 1H), 5.18 (d, *J* = 7.2 Hz, 1H), 2.37 (s, 3H). $^{13}$C NMR δ 143.2, 140.5, 137.3, 129.3, 128.5, 127.5, 127.3, 127.2, 61.3, 21.5.

**4-Methyl-*N*-(phenyl(*p*-tolyl)methyl)benzenesulfonamide:** $^{1}$H NMR δ 7.56 (d, *J* = 8.4

Hz, 2H), 7.21-7.20 (m, 3H), 7.14-7.10 (m, 4H), 7.02-6.96 (m, 4H), 5.52 (d, *J* = 7.8 Hz, 1H), 5.10 (d, *J* = 7.2 Hz, 1H), 2.38 (s, 3H), 2.28 (s, 3H). $^{13}$C NMR δ 143.2, 140.5, 137.3, 129.3, 128.5, 127.5, 127.3, 127.2, 61.3, 21.5, 21.0.

**4-Methyl-N-(phenyl(*o*-tolyl)methyl)benzenesulfonamide:** $^{1}$H NMR δ 7.55 (d, *J* = 7.8 Hz, 2H), 7.21-7.19 (m, 3H), 7.13-7.10 (m, 4H), 7.06-7.05 (m, 4H), 5.80 (d, *J* = 7.2 Hz, 1H), 5.10 (d, *J* = 6.6 Hz, 1H), 2.37 (s, 3H), 2.16 (s, 3H). $^{13}$C NMR δ 143.2, 140.0, 138.2, 137.4, 135.5, 130.6, 129.3, 128.5, 127.6, 127.5, 127.2, 127.1, 126.1, 58.1, 21.5, 19.3.

***N*-((4-Methoxyphenyl)(phenyl)methyl)-4-methylbenzenesulfonamide:** $^{1}$H NMR δ 7.56 (d, *J* = 7.8 Hz, 2H), 7.22-7.17 (m, 3H), 7.14-7.10 (m, 4H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 5.52 (d, *J* = 6.6 Hz, 1H), 5.09 (d, *J* = 7.2 Hz, 1H), 3.75 (s, 3H), 2.38 (s, 3H). $^{13}$C NMR δ 160.0, 143.1, 140.7, 137.4, 132.7, 129.3, 128.6, 128.5, 127.4, 127.3, 127.2, 60.8, 55.2, 21.5.

**N-((4-Chlorophenyl)(phenyl)methyl)-4-methylbenzenesulfonamide:** 1H NMR δ 7.54 (d, J = 8.4 Hz, 2H), 7.20-7.19 (m, 3H), 7.17-7.12 (m, 4H), 7.06-7.04 (m, 4H), 5.53 (d, J = 7.2 Hz, 1H), 5.41 (d, J = 7.2 Hz, 1H), 2.38 (s, 3H). 13C NMR δ 143.4, 140.0, 139.0, 137.2, 133.4, 129.4, 128.8, 128.7, 128.6, 127.8, 127.2, 127.1, 60.7, 21.5.

# Chapter 4. Rhodium-Catalyzed Addition Reaction of Arylborons with Ketones

## 4.1 Introduction

Over the past decade, transition metal-catalyzed addition reactions of organoborons with aldehydes to prepare secondary alcohols have achieved enormous success.[6,7,10,28b,31c,38,15a,10t,16,19,39] However, 1,2-addition reactions of much less reactive ketones with organoborons to prepare tertiary alcohols are largely limited to activated substrates and intramolecular reactions or must be preceded by boron-to-zinc transmetalation.[7f,8a,40] In fact, to our best knowledge, only one recent report described the 1,2-addition reactions of arylboronic acids with unactivated ketones catalyzed by Ni(II)/*N*-heterocarbene complexes through an oxanickelacycle intermediate. The reason why $d^8$ metal catalysts [Rh(I), Pd(II)] cannot efficiently catalyze such addition reactions is partly due to faster decomposition of catalyst after transmetalation occurred under widely employed hydrous condition.

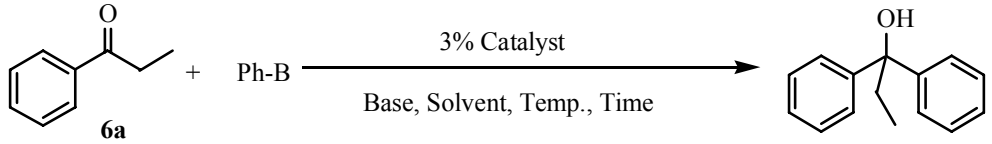
We have recently developed palladacycle **1**-**3**, platinacycle **4** and $[Rh(COD)Cl]_2$ **5** as highly active catalysts for the addition reaction of arylboronic acids with carbonyl-containing compounds. In the previous chapter, we described that the palladacycle-catalyzed addition reactions of arylboroxines with aldehydes could occur via non-transmetalation pathway under anhydrous condition with an extremely low catalyst loading and the presence of water played a detrimental role for the catalyst longevity. We thus surmised that under an anhydrous condition with minimizing the catalyst decomposition, we might successfully employ such catalysts to catalyze the 1,2-addition reaction of organoborons with less reactive ketones. In this chapter, we will

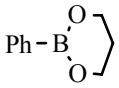
report the first Rh-catalyzed 1,2-addition reaction of arylboroxines with unactivated ketones including asymmetric version to prepare tertiary alcohol.

## 4.2 Exploring the Reaction Condition of Transition Metal-Catalyzed Addition Reaction of Arylborons with Ketones

To explore the possibility of transition metal-catalyzed addition reaction of arylborons with ketones, our study began with testing several transition metal complexes for the addition reaction of phenylboroxine with propiophenone under anhydrous condition. By using dry base and dry phenylboronic acid (phenylboroxine), we found that palladacycle **3** and platinacycle **4** were low efficiency for such addition reaction, catalysts decomposition was observed in less than 5 minutes. To our pleasure, $[Rh(COD)Cl]_2$ **5** exhibited promising catalytic activity, even though along with the decomposition of catalyst, as Rh black was observed in 10 minutes at 90 $^oC$ (Table 3.1, entry 1-3). Further study revealed that toluene was the best solvent and both $K_2CO_3$ and $K_3PO_4$ were the best bases (Table 4.1, entry 3-9). Although a high reaction temperature can improve the reaction rate, it can also accelerate the decomposition of catalyst as result of reaction slowing down or even ceasing (Table 4.1, entry 4, 10-12). In comparison, the addition product was obtained only in 51% conversion by using untreated commercial available phenylboronic acid (about 70% as the form of phenylboroxine) and an even less conversion with more phenylboronic acids in the reaction system (Table 4.1, entry 15-16). Less reactivity was observed with 2-phenyl-1,3,2-dioxaborinane in the presence of $[Rh(COD)Cl]_2$ **5** (4% conversion, Table 4.1, entry 14).

**Table 4.1** Transition Metal-Catalyzed 1,2-Addition Reaction of Phenylboron Reagents with Propiophenone




| entry | catalyst | Ph-B | base | solvent | temp.($^oC$) | time | conversion(%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | **3** | $(PhBO)_3$ | $K_2CO_3$ | Toluene | 50 | 5h | 12 |
| 2 | **4** | $(PhBO)_3$ | $K_3PO_4$ | Toluene | 90 | 5h | 4 |
| 3 | **5** | $(PhBO)_3$ | $K_3PO_4$ | Toluene | 90 | 2h | 77 |
| 4 | **5** | $(PhBO)_3$ | $K_2CO_3$ | Toluene | 90 | 2h | 79 |
| 5 | **5** | $(PhBO)_3$ | KF | Toluene | 90 | 2h | 70 |
| 6 | **5** | $(PhBO)_3$ | $Cs_2CO_3$ | Toluene | 90 | 2h | 32 |
| 7 | **5** | $(PhBO)_3$ | $K_2CO_3$ | THF | 70 | 2h | 7 |
| 8 | **5** | $(PhBO)_3$ | $K_2CO_3$ | $CH_2ClCH_2Cl$ | 90 | 2h | 3 |
| 9 | **5** | $(PhBO)_3$ | $K_2CO_3$ | Dioxane | 90 | 2h | 25 |
| 10 | **5** | $(PhBO)_3$ | $K_2CO_3$ | Toluene | r.t. | 2h | 7 |
| 11 | **5** | $(PhBO)_3$ | $K_2CO_3$ | Toluene | 60 | 2h | 25 |
| 12 | **5** | $(PhBO)_3$ | $K_2CO_3$ | Toluene | 110 | 2h | 63 |
| 13 | **5** | $(PhBO)_3$ | $K_2CO_3$ | Toluene | 90 | 5h | 99 |
| 14 | **5** |  | $K_2CO_3$ | Toluene | 90 | 2h | 4 |
| 15 | **5** | $PhB(OH)_2$ | $K_2CO_3$ | Toluene | 90 | 2h | 51[c] |
| 16 | **5** | $(PhBO)_3$ | $K_2CO_3$ | Toluene | 90 | 2h | 20[d] |

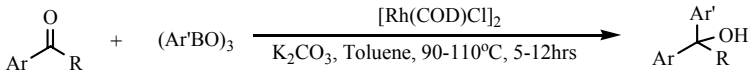
a. Reaction conditions: propiophenone (0.25mmol), Ph-B(2 equiv), Base(3 equiv), solvent (1ml), 3% of Pd, Pt or Rh, temperature; b. Result by GC-MS; c. Untreated phehylboronic acid; d. 6 equiv.of $H_2O$ as additive

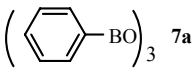
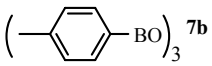
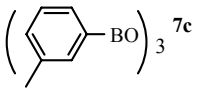
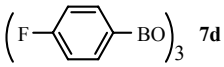
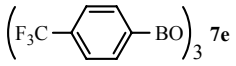
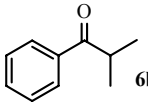
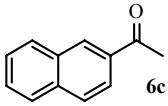
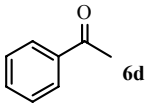
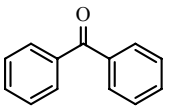
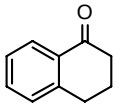
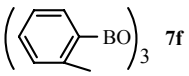
## 4.3 Determine the Reaction Scope of Rh-Catalyzed Addition Reaction of Arylborons with Ketones

With toluene as solvent and $K_2CO_3$ as base, we employed **5** as catalyst for the addition reactions of a number of arylketones and arylboroxines, and our results are listed in Table 4.2. Unactivated diaryl and alkyl aryl ketones react with different arylboroxines to give corresponding tertiary alcohol in good to excellent yields. The electronic nature of phenyl ring of boroxines showed no obvious effect on this addition reaction. But the substituent with steric hindrance on arylboroxines did affect addition reaction significantly as much lower conversion was observed with *o*-tolylboroxine as the reagent(Table 4.2, entry 15).

We also found that aliphatic ketones including cyclic and acyclic alkyl ketones were suitable substrates for 1,2-addition reaction with arylboroxines and alkyl aryl tertiary alcohols were obtained in good yields (Table 4.3, entry 1-10). The aldol condensation between alkyl ketones was not observed under this reaction condition. In comparison, cyclic alkyl ketones are more reactive than acyclic ones for such addition reaction. The substituent on arylboroxines including steric hindrance one did not affect addition reaction significantly.

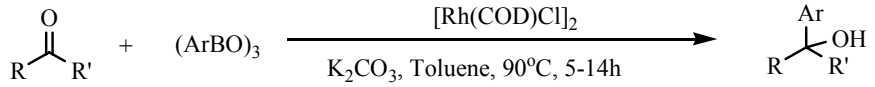
**Table 4.2** $[Rh(COD)Cl]_2$-Catalyzed Addition Reactions of Arylboroxines with Arylketones

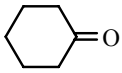
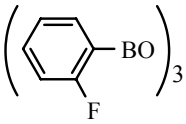
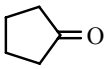
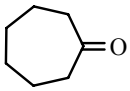
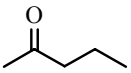
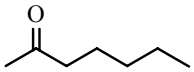
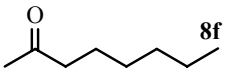



| entry | ArC(O)R' | $(Ar'BO)_3$ | catalyst loading(%) | temp.(°C) | yield(%)[b] |
|---|---|---|---|---|---|
| 1 | **6a** |  **7a** | 1.5 | 90 | 88 |
| 2 | **6a** |  **7b** | 1.5 | 90 | 92 |
| 3 | **6a** |  **7c** | 1.5 | 90 | 90 |
| 4 | **6a** |  **7d** | 1.5 | 90 | 80 |
| 5 | **6a** |  **7e** | 1.5 | 90 | 87 |
| 6 |  **6b** | **7a** | 1.5 | 90 | 82 |
| 7 |  **6c** | **7a** | 1.5 | 110 | 90 |
| 8 | **5c** | **7c** | 1.5 | 110 | 86 |
| 9 |  **6d** | **7a** | 2.5 | 110 | 88 |
| 10 | **6d** | **7c** | 2.5 | 110 | 90 |
| 11 |  **6e** | **7a** | 2.5 | 110 | 80 |
| 12 | **6e** | **7c** | 2.5 | 110 | 85 |
| 13 | **6e** | **7d** | 2.5 | 110 | 88 |
| 14 |  **6f** | **7b** | 2.5 | 70 | 61[c] |
| 15 | **6a** |  **7f** | 2.5 | 110 | <5 |

a. Reaction conditions: ketone (0.25mmol), arylboroxine (2 equiv), $K_2CO_3$(3 equiv), toluene (1ml), catalyst (1.5-2.5%), 90-110°C, 5-12 hours; b. Isolated yield; c. 78%conversion for 24h

**Table 4.3** $[Rh(COD)Cl]_2$-Catalyzed Addition Reactions of Arylboroxines with Alkylketones




| entry | RC(O)R' | $(ArBO)_3$ | catalyst loading(%) | yield(%)[b] |
|---|---|---|---|---|
| 1 |  **8a** | **7a** | 1.5 | 91 |
| 2 | **8a** | **7c** | 1.5 | 90 |
| 3 | **8a** | **7d** | 1.5 | 88 |
| 4 | **8a** |  **7g** | 1.5 | 86 |
| 5 |  **8b** | **7c** | 1.5 | 82 |
| 6 |  **8c** | **7a** | 2.5 | 80 |
| 7 |  **8d** | **7a** | 2.5 | 81 |
| 8 |  **8e** | **7a** | 2.5 | 84 |
| 9 |  **8f** | **7a** | 2.5 | 83 |
| 10 | **8f** | **7c** | 2.5 | 87 |

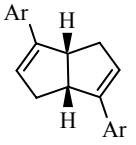
a. Reaction conditions: ketone (0.25mmol), arylboroxine (2 equiv), $K_2CO_3$(3 equiv), toluene (1ml), catalyst (1.5-2.5%), 90°C, 5-14 hours; b. Isolated yield

## 4.4 Rh/Chiral Diene Ligand-Catalyzed Asymmetric Addition Reaction of Arylborons with Ketones

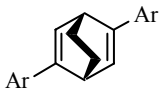
We next examined the possibility of asymmetric synthesis of tertiary alcohols by Rh-catalyzed 1,2-addition reaction of arylboron reagents with ketones. Most recently,

$C_2$-symmetric chiral diene ligands for asymmetric Rhodium catalysts have been well employed in the addition reactions of arylboronic acids with aldimines and ketoimines. Therefore, we surmised that these chiral diene ligands may also serve as good ligands for asymmetric addition reactions of arylboronic acids with ketones. Very gratifyingly, Rh/chiral diene ligand complex-catalyzed addition reaction occurred smoothly even at room temperature and afforded moderate enantioselectivity. Replacing the aryl units in **9a** by more steric hindrance and electron-withdrawing groups (**9b**, **9c**) can both improve the reaction rate and enantioselectivity significantly. Since the $CF_3$ group on diene largely decrease the electron-donating ability of diene, the Rh(I) center change to be more Lewis acidic and thus more active. Therefore, the reaction can occur smoothly at non-unhydrous condition (regular arylboronic acid, base and solvent) without fast catalyst decomposing. Further examination revealed that base can only effect the reaction rate but not for enantioselectivity of product. Both *o*-xylene and *p*-xylene can slightly improve the enantioselectivity comparing to toluene and benzene. Lowering the reaction temperature to $0^oC$, the enantioselectivity of product can be increased. Rh/diene ligands **10a**, **10b** complexes were not efficient catalysts for addition reactions of arylborons with ketones.

**Figure 4.1** $C_2$-Symmetric Chiral Dienes

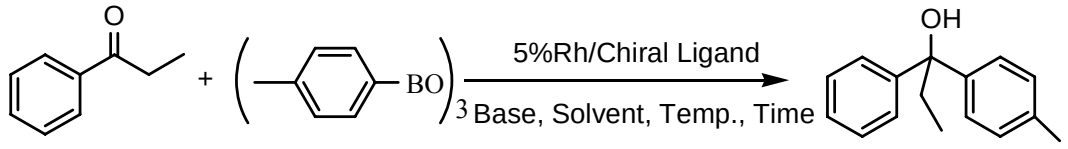



(3aR,6aR)-**9a** Ar = Ph
**9b** Ar = 4-*t*-Bu-Ph
**9c** Ar = 4-$CF_3$-Ph




(1aR, 4aR)-**10a** Ar = 4-*t*-Bu-Ph
**10b** Ar = 4-$CF_3$-Ph

**Table 4.4** Rh(I)/Chiral Diene-Catalyzed Addition Reaction of Phenylboroxine with Propiophenone

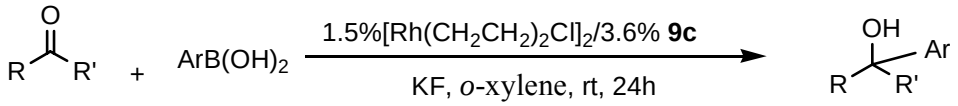


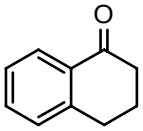
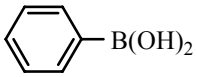
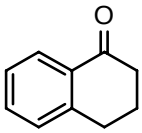
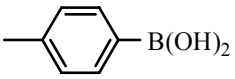
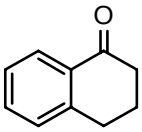
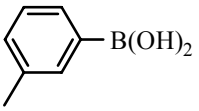
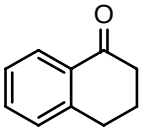
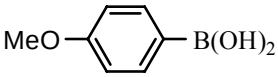
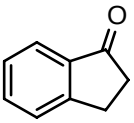
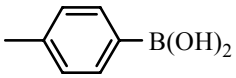
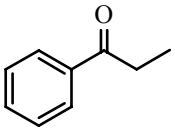
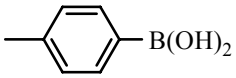
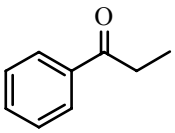
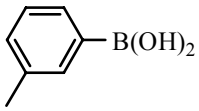

| entry | ligand | base | solvent | temp.($^o$C) | time(h) | yield(%)[b] | ee[c] |
|---|---|---|---|---|---|---|---|
| 1 | **9a** | $K_2CO_3$ | Toluene | 60 | 48 | 87 | 16 |
| 2 | **9b** | $K_2CO_3$ | Toluene | 60 | 48 | 88 | 25 |
| 3 | **9c** | $K_2CO_3$ | Toluene | 60 | 20 | 87 | 34 |
| 4 | **9c** | $K_2CO_3$ | Toluene | 60 | 12 | 88 | 34[d] |
| 5 | **9c** | $K_2CO_3$ | Toluene | r.t. | 38 | 88 | 40[d] |
| 6 | **9c** | $K_3PO_4$ | Toluene | r.t. | 38 | 70 | 40[d] |
| 7 | **9c** | KF | Toluene | r.t. | 30 | 89 | 40[d] |
| 8 | **9c** | KF | Benzene | r.t. | 30 | 85 | 36[d] |
| 9 | **9c** | KF | *o*-Xylene | r.t. | 30 | 87 | 41[d] |
| 10 | **9c** | KF | *o*-Xylene | r.t. | 30 | 88 | 41[e] |
| 11 | **10a** | KF | *o*-Xylene | r.t. | 30 | 15 | 18[e,f] |
| 12 | **10b** | KF | *o*-Xylene | r.t | 30 | - | -[e,g] |
| 13 | **9c** | KF | *o*-Xylene | 0 | 96 | 88 | 47[e] |

a. Reaction conditions: ketone (0.125mmol), phenylboroxine (2 equiv), base (3 equiv), toluene (1ml), catalyst (2.5%), Ligand (6.0%); d. 2eq $H_2O$; e.Untreated commercial *p*-tolylboronic acid(about 70% of phenylboroxine); f. Only 24% conversion; g. No reaction

With optimized reaction condition, we test asymmetric addition reaction of arylboronic acids with 1-tetralone or propiophenone. The best enantioselectivity was achieved as 68% by the addition reaction of 1-tetralone with *p*-tolylboronic acids at 0 $^o$C. To our knowledge, this is the best enantioselective tertiary alcohol prepared by the reaction of arylborons with ketone.

**Table 4.5** Rh(I)/Chiral Diene-Catalyzed Addition Reaction of Arylboronic Acids with Ketones




| entry | ketone | $ArB(OH)_2$ | yield(%)[b] | ee[c] |
|---|---|---|---|---|
| 1 |  |  | 81 | 36(R) |
| 2 |  |  | 80 | 62(68)[d] |
| 3 |  |  | 84 | 43 |
| 4 |  |  | 84 | 49[e] |
| 5 |  |  | 83 | 56 |
| 6 |  |  | 83 | 42(47)[d] |
| 7 |  |  | 85 | 39 |

a. Reaction conditions: ketone (0.25 mmol), arylbornic acid (2 equiv), KF (3 equiv), *o*-xylene (1ml), $[Rh(CH_2CH_2)_2Cl]_2$ (1.5%), Ligand (3.6%); b. Isolated yield; e. c Determined by HPLC analysis (Chiral OD Column); d. In parentheses: reported ee value with 5 mol % Rh/ 6mol % ligand at 0 $^oC$ for 7days; g. Reacted at 60$^oC$ for 20h;

In summary, we have disclosed that rhodium/diene complexes can effectively

catalyzed the addition of ketones with arylboroxines including the asymmetric version. This work may pave the road for the development of $d^8$ transition metal catalyzed-addition reaction of organoborons with ketones. Our future work will be directed to improve the enantioselectivity of such addition reactions.

## 4.5 Experimental Section

**General**: NMR spectra were recorded on Varian 300MHz or 600MHz spectrometers. Elemental analysis was carried out by Altantic Microanalysis, Inc., Norcross, GA. High resolution mass spectra (HRMS) were acquired by Agilent G6520 Q-TOF mass spectrometer. All yields reported refer to isolated yields unless otherwise indicated, and the product purity was estimated to be greater than 95% as determined by $^1$H NMR. Compounds described in the literature were characterized by comparison of their $^1$H NMR and $^{13}$C NMR spectra to reported data.

All the toluene we used was dried and freshly distilled with sodium prior to use. Arylboronic acids were obtained as gifts from Frontier Scientific, Inc. The palladacycle complexes were prepared according to the reported method.[1]

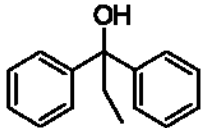
The dried bases ($K_3PO_4$ and $K_2CO_3$) were achieved by baking well-ground base powder at 140$^o$C under vacuum for 6 hours.

All arylboroxines were prepared by azeotropic distillation of arylboronic acids with dry toluene for 6 hours. The product purity was estimated to be greater than 95% as determined by $^1$H NMR.

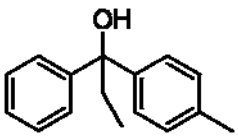
Other chemical reagents were purchased from Strem Chemicals, Aldrich or Alpha

Aesar and used directly.

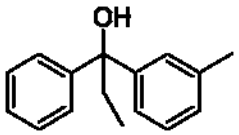
**General procedure for $[Rh(COD)Cl]_2$-catalyzed addition reactions of arylboroxines with ketones:** To a vial containing ketone (0.25 mmol), arylboroxine (0.5 mmol), $K_2CO_3$ or $K_3PO_4$ (0.75 mmol) and $[Rh(COD)Cl]_2$ (0.00375-0.00625 mmol) was added toluene (1 ml). After the mixture was stirred at 90-110 $^oC$ for 5-14 hours, the reaction was quenched by adding 4 N HCl (2 mL) aqueous solution. The mixture was extracted with $CH_2Cl_2$ (3 x15 mL). The organic layers were combined. After evaporation of the organic solvents, the residue was subjected to column chromatography [silica gel, ethyl acetate/hexane (v/v=1:20) as eluent] to afford the products.



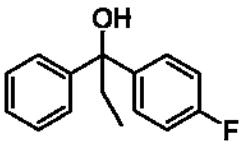

**1,1-Diphenylpropan-1-ol** $^1H$ NMR ($CDCl_3$, 600 MHz) δ 7.40 (d, *J* = 7.2 Hz, 4H), 7.29 (t, *J* = 7.2 Hz, 4H), 7.20 (t, *J* = 7.2 Hz, 2H), 2.31 (q, *J* = 7.2 Hz, 2H), 2.09 (s, 1H), 0.87 (t, *J* = 7.2 Hz, 3H). $^{13}C$ NMR ($CDCl_3$, 150 MHz) δ 146.9, 128.1, 126.7, 126.1, 78.4, 34.4, 8.1.



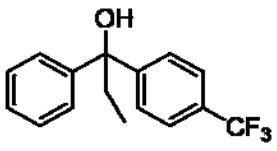

**1-Phenyl-1-*p*-tolylpropan-1-ol** Light yellow oil. $^1H$ NMR ($CDCl_3$, 600 MHz) δ 7.40 (d, *J* = 7.8 Hz, 2H), 7.30-7.28 (m, 4H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 2.31(s, 3H), 2.29 (q, *J* = 7.2 Hz, 2H), 2.04 (s, 1H), 0.87 (t, *J* = 7.2 Hz, 3H). $^{13}C$ NMR ($CDCl_3$, 150 MHz) δ 147.0, 144.0, 136.3, 128.8, 128.0, 126.6, 126.0, 126.0, 78.3, 34.4, 20.9, 8.2. IR (neat, $cm^{-1}$) 3463(br), 3025(w), 2972(w), 2937(w), 2878(w), 1493(m), 699(s). HR-MS (+ESI): calcd. for $C_{16}H_{18}NaO$ $[M+Na]^+$ 249.1250, found 249.1248.




**1-Phenyl-1-*m*-tolylpropan-1-ol** Light yellow oil. $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.40 (d, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.24(s, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 5.4 Hz, 2H), 7.03-7.02 (m, 1H), 2.31(s, 3H), 2.29 (q, *J* = 7.2 Hz, 2H), 2.07 (s, 1H), 0.87 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 146.9, 146.8, 137.6, 128.0, 127.9, 127.5, 126.7, 126.6, 126.0, 123.1, 78.4, 34.4, 21.6, 8.1. IR (neat, $cm^{-1}$) 3465(br), 3026(w), 2972(w), 2878(w), 1447(m), 756(m), 699(s). HR-MS (+ESI): calcd. for $C_{16}H_{18}NaO$ $[M+Na]^+$ 249.1250, found 249.1248.

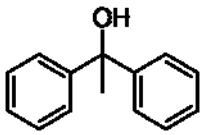



**1-(4-Fluorophenyl)-1-phenylpropan-1-ol** Light yellow oil.$^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.39-7.35 (m, 4H), 7.30 (t, *J* = 8.4 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.97 (t, *J* = 8.4 Hz, 1H), 2.37-2.24 (m, 2H), 2.06 (s, 1H), 0.86 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 161.6 (d, *J* = 244.4Hz, 1C), 146.7, 142.6 (d, *J* = 3.3Hz, 1C), 128.2, 127.8 (d, *J* = 8.4 Hz, 1C), 126.9, 126.0, 114.7 (d, *J* = 21.2 Hz, 1C), 78.1, 34.5, 8.1. $^{19}$F NMR (282 MHz) δ: -117.0. IR (neat, $cm^{-1}$) 3462(br), 3061(w), 2974(w), 2941(w), 2880(w), 1507(s),1223(m), 1160(m), 831(s), 699(s). HR-MS (+ESI): calcd. for $C_{16}H_{15}FNaO$ $[M+Na]^+$ 253.0999, found 253.0998.

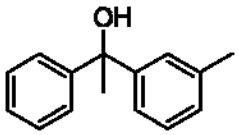



**1-Phenyl-1-(4-(trifluoromethyl)phenyl)propan-1-ol** Light yellow oil. $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.56-7.52 (m, 4H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.26-7.25 (m, 1H), 2.37-2.29 (m, 2H), 2.09 (s, 1H), 0.88 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 150.7, 146.2, 128.9 (q, *J* = 31.8 Hz, 1C), 128.4, 127.2, 126.4, 126.0, 125.0 (q, *J* = 3.9Hz),

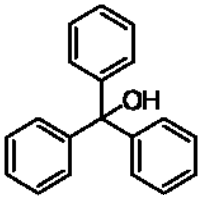
124.2 (q, $J$ = 270.6 Hz), 78.2, 34.3, 8.0. $^{19}$F NMR (282 MHz) δ: -63.1. IR (neat, cm$^{-1}$) 3468(br), 2976(w), 2930(w), 1326(s), 1165(m), 1124(m), 1017(m). HR-MS (+ESI): calcd. for $C_{16}H_{15}F_3NaO$ $[M+Na]^+$ 303.0967, found 303.0968.



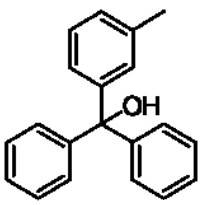

**1,1-Diphenylethanol** $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.41 (d, $J$ = 7.8 Hz, 4H), 7.30 (t, $J$ = 7.2 Hz, 4H), 7.23 (t, $J$ = 7.8 Hz, 2H), 2.21 (s, 1H), 1.94 (s, 3H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 148.0, 128.1, 126.9, 125.8, 76.2, 30.8.




**1-Phenyl-1-*m*-tolylethanol** $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.40 (d, $J$ = 7.8 Hz, 2H), 7.30 (t, $J$ = 7.8 Hz, 2H), 7.23(s, 1H), 7.22-7.18 (m, 3H), 7.05-7.04 (m, 1H), 2.32(s, 3H), 2.21 (s, 1H), 1.92 (s, 3H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 148.0, 147.9, 137.7, 128.1, 128.0, 127.7, 126.8, 126.5, 125.8, 122.9, 76.1, 30.8, 21.6.

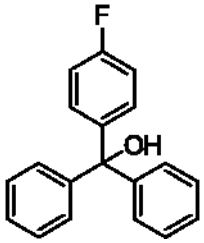



**Triphenylmethanol** $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.30-7.24 (m, 15H), 2.82 (s, 1H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 146.8, 127.9, 127.2, 82.0.

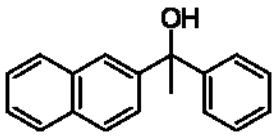



**Diphenyl(*m*-tolyl)methanol** $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.30-7.24 (m, 10H), 7.17 (t, $J$ = 7.8 Hz, 1H), 7.13 (s, 1H), 7.07 (d, $J$ = 7.2 Hz, 1H), 7.00 (d, $J$ = 8.4 Hz, 1H), 2.81 (s, 1H), 2.29 (s, 3H).

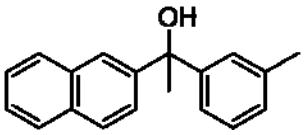
$^{13}$C NMR ($CDCl_3$, 150 MHz) δ 146.9, 146.8, 137.5, 128.4, 128.0, 127.9, 127.8, 127.7, 127.1, 125.1, 82.0, 21.6.




**(4-Fluorophenyl)diphenylmethanol** $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.31-7.22 (m, 12H), 6.99-6.95 (m, 2H), 7.17 (t, *J* = 7.8 Hz, 1H), 2.81 (s, 1H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 161.9 (d, *J* = 244.8Hz), 146.7, 142.6 (d, *J* = 3.3Hz), 129.7 (d, *J* = 7.8Hz), 128.0, 127.8, 127.4, 114.6 (d, *J* = 21.2Hz), 81.6. 19F NMR (282 MHz) δ: -116.1

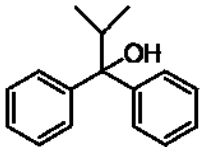



**1-(Naphthalen-2-yl)-1-phenylethanol** $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.94 (s, 1H), 7.81 (d, *J* = 7.2 Hz, 1H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.46-7.41 (m, 4H), 7.38 (d, *J* = 8.4Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 2H), 7.23-7.19 (m, 1H), 2.33 (s, 3H), 2.00 (s, 3H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 147.7, 145.2, 132.9, 132.3, 128.2, 128.1, 127.9, 127.5, 127.0, 126.1, 125.9, 124.9, 123.7, 76.3, 30.7.

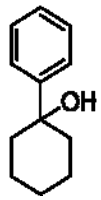



**1-(Naphthalen-2-yl)-1-*m*-tolylethanol** Light yellow oil. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.97 (s, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.48-7.43 (m, 2H), 7.40 (dd, *J* = 9.0Hz, 2.4Hz, 1H), 7.26 (s, 1H), 7.23-7.18 (m, 2H), 7.06 (d, *J* = 7.2 Hz, 1H), 2.31 (s, 3H), 2.28 (s, 1H), 2.02 (s, 3H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 147.7, 145.3, 137.8, 133.0, 132.3, 128.2, 128.1, 127.9, 127.8, 127.5, 126.6, 126.1, 125.9, 125.0, 123.6, 123.0, 76.3, 30.7, 21.6. IR (neat, $cm^{-1}$) 3428(br), 3055(w), 2978(w), 819(s), 790(s),

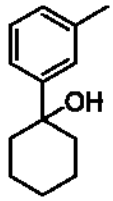
706(s). HR-MS (+ESI): calcd. for $C_{19}H_{18}NaO$ $[M+Na]^+$ 253.0999, found 253.0998.



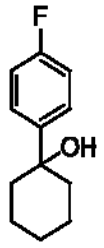

**2-Methyl-1,1-diphenylpropan-1-ol** $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.50 (d, *J* = 7.2 Hz, 4H), 7.28 (t, *J* = 7.2 Hz, 4H), 7.16 (t, *J* = 7.2 Hz, 2H), 2.89 (m, *J* = 6.6 Hz, 1H), 2.03 (s, 1H), 0.90 (s, 3H), 0.88 (s, 3H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 146.7, 128.1, 126.3, 125.7, 80.4, 35.0, 17.2.



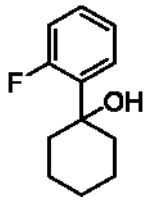

**1-Phenylcyclohexanol** $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.50 (d, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 1.86-1.81 (m, 2H), 1.78-1.72 (m, 5H), 1.66-1.62 (m, 3H), 1.32-1.26 (m, 1H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 149.4, 128.2, 126.6, 124.5, 73.1, 38.8, 25.5, 22.1.



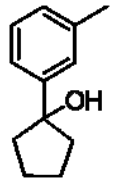

**1-*m*-Tolylcyclohexanol** $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.33 (s, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 1H), 2.36 (s, 3H), 1.85-1.81 (m, 2H), 1.79-1.75 (m, 5H), 1.66-1.61 (m, 2H), 1.60 (s, 1H), 1.32-1.26 (m, 1H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 149.4, 137.7, 128.1, 127.4, 125.3, 121.5, 73.1, 38.8, 25.5, 22.2, 21.6.



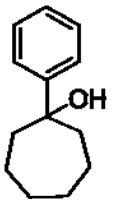

**1-(4-Fluorophenyl)cyclohexanol**[10] $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.48-7.44 (m, 2H), 7.01 (t, *J* = 7.2 Hz, 2H), 1.83-1.70 (m, 5H), 1.66 (s, 1H), 1.65-1.62 (m, 2H), 1.32-1.25 (m, 1H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ161.6 (d, *J* = 243.3Hz), 145.1 (d, *J* = 2.9Hz), 126.3 (d, *J* = 7.8Hz), 114.8 (d, *J* = 20.6Hz), 72.8, 38.9, 25.4, 21.1. $^{19}$F NMR (282 MHz) δ: -117.4. HR-MS (+ESI): calcd. for $C_{12}H_{15}FNaO$ $[M+Na]^+$ 217.0999, found 217.1003.



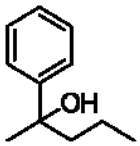

**1-(2-Fluorophenyl)cyclohexanol** White solid. $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.55 (t, *J* = 7.8 Hz, 1H), 7.24-7.20 (m, 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.03-7.00 (m, 1H), 2.07-2.01 (m, 3H), 1.81-1.73 (m, 5H), 1.64-1.62 (m, 2H), 1.35-1.28 (m, 1H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ160.4 (d, *J* = 243.9Hz), 135.8 (d, *J* = 10.7Hz), 128.4 (d, *J* = 8.9Hz), 126.7 (d, *J* = 4.5Hz), 124.0 (d, *J* = 3.3Hz), 116.2 (d, *J* = 24.0Hz), 72.6 (d, *J* = 3.3Hz), 36.7 (d, *J* = 3.3Hz), 25.3, 21.8. $^{19}$F NMR (282 MHz) δ: -113.7. IR (neat, $cm^{-1}$) 3427(br), 3060(w), 2971(w), 1508(m), 1447(m), 785(s), 702(s). HR-MS (+ESI): calcd. for $C_{12}H_{15}FNaO$ $[M+Na]^+$ 217.0999, found 217.0998.



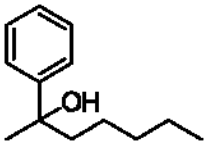

**1-*m*-Tolylcyclopentanol** Colorless oil. $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.32 (s, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 2.37 (s, 3H), 2.02-1.97 (m, 6H), 1.86-1.81 (m, 2H), 1.54 (s, 1H), 1.32-1.26 (m, 1H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 147.0, 137.8, 128.1, 127.5, 125.9, 122.1, 83.4, 41.8, 23.8, 21.6. IR (neat, $cm^{-1}$) 3384(br), 2966(m), 2871(w), 1041(m), 762(s), 703(s). HR-MS (+ESI): calcd. for $C_{12}H_{16}NaO$ $[M+Na]^+$ 199.1093, found 199.1090.



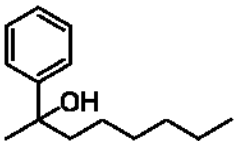

**1-Phenylcycloheptanol**[8] $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.50 (d, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 2.09-2.05 (m, 2H), 1.92-1.88 (m, 2H), 1.84-1.78 (m, 2H), 1.76-1.70 (m, 2H), 1.66 (s, 1H), 1.63-1.56 (m, 4H). $^{13}$C NMR ($CDCl_3$, 150 MHz) 150.7, 128.1, 126.5, 124.4, 76.8, 43.2, 29.1, 22.5.



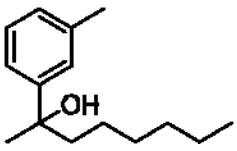
**2-Phenylpentan-2-ol**[11] $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 1.83-1.75 (m, 2H), 1.73 (s, 1H), 1.55 (s, 3H), 1.32-1.26 (m, 1H), 1.19-1.14 (m, 1H), 0.86 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 148.0, 128.1, 126.4, 124.7, 74.7, 46.5, 30.1, 17.3, 14.4.



**2-Phenylheptan-2-ol**[12] $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.43 (d, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 1.84-1.75 (m, 2H), 1.71 (s, 1H), 1.55 (s, 3H), 1.30-1.21 (m, 5H), 1.16-1.11 (m, 1H), 0.83 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 148.1, 128.1, 126.4, 124.7, 74.7, 44.1, 32.1, 30.1, 23.6, 22.5, 14.0.



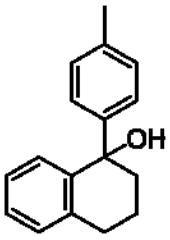
**2-Phenyloctan-2-ol** Light yellow oil. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.43-7.41 (m, 2H), 7.35-7.32 (m, 2H), 7.25-7.21 (m, 1H), 1.82-1.75 (m, 2H), 1.70 (s, 1H), 1.55 (s, 3H), 1.23-1.21 (m, 7H), 1.16-1.11 (m, 1H), 0.84-0.82 (m, 3H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 148.0, 128.1, 126.4, 124.7, 74.7, 44.2, 31.7, 30.1, 29.6, 23.9, 22.6, 14.0. IR (neat, $cm^{-1}$) 3401(br), 3060(m), 2933(m), 2860(w), 764(m), 699(s). HR-MS (+ESI): calcd. for $C_{14}H_{22}NaO$ $[M+Na]^+$ 229.1563, found 229.1562.



**2-*m*-Tolyloctan-2-ol** Light yellow oil. $^1$H NMR ($CDCl_3$, 600 MHz) δ7.25 (s, 1H), 7.23-7.19 (m, 2H), 7.04 (d, *J* = 7.2 Hz, 1H), 2.36 (s, 3H), 1.82-1.73 (m, 2H), 1.72 (s, 1H), 1.53 (s, 3H),

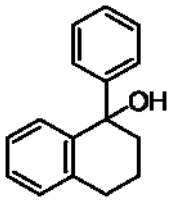
1.28-1.20 (m, 7H), 1.16-1.11 (m, 1H), 0.85 (m, 3H). $^{13}C$ NMR ($CDCl_3$, 150 MHz) δ 148.1, 137.6, 128.0, 127.2 125.5, 121.8, 74.7, 44.2, 31.7, 30.1, 29.6, 23.9, 22.6, 21.6, 14.0. IR (neat, $cm^{-1}$) 3410(br), 2935(m), 2861(w), 785(m), 706(s). HR-MS (+ESI): calcd. for $C_{15}H_{24}NaO$ $[M+Na]^+$ 243.1719, found 243.1719.

**General procedure for Rh/chiral diene ligand-catalyzed addition reactions of arylboroxines with ketones:** In glovebox, to a vial containing $[Rh(CH_2CH_2)_2Cl]_2$ (0.00375 mmol) and chiral diene ligand **9a**, **9b** or **9c** (0.0045mmol, the preparation of these ligand refer the literature 13) was added *o*-xylene (0.2ml) and stirred for 15 min. To another vial containing ketone (0.25 mmol), arylboroxine (0.5 mmol) and KF (0.75 mmol) was added *o*-xylene (0.6 ml). Then transferred the pre-stirred catalyst solution into the vial containing raw materials and rinsed the vial by another 0.2 ml of *o*-xylene. After the mixture was stirred at room temperature or 0 $^oC$ for 20-168 hours, the reaction was quenched by adding 4 N HCl (2 mL) aqueous solution. The mixture was extracted with $CH_2Cl_2$ (3 x15 mL). The organic layers were combined. After evaporation of the organic solvents, the residue was subjected to column chromatography [silica gel, ethyl acetate/hexane (v/v=1:20) as eluent] to afford the products.

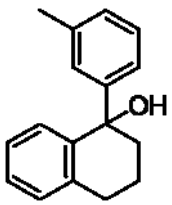



**1-*p*-Tolyl-1,2,3,4-tetrahydronaphthalen-1-ol** Colorless oil, 80% yield. $[\alpha]_D$ = +21.82 ($CHCl_3$, c = 0.267, 29$^oC$). 68% ee. [HPLC condition: Chiralcel OD column, n-hexane/2-propanol = 98.5/1.5, 1.0 ml/min, 230 nm UV detector, t= 12.85 min for the isomer in major amount and t = 22.52 min for the isomer in minor amount]. $^1H$ NMR ($CDCl_3$, 600

MHz) δ 7.22-7.17 (m, 3H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.11-7.09 (m, 3H), 7.04 (d, *J* = 7.2 Hz, 1H), 2.91-2.82 (m, 2H), 2.32 (s, 3H), 2.17 (s, 1H), 2.13-2.07 (m, 2H), 2.01-1.94 (m, 1H), 1.79-1.72 (m, 1H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 146.0, 142.1, 137.5, 136.1, 128.8, 128.7, 128.4, 127.4, 126.4, 126.3, 75.2, 41.4, 29.8, 21.0, 19.6.

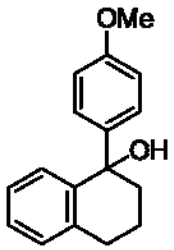



**1-Phenyl-1,2,3,4-tetrahydronaphthalen-1-ol** Colorless oil, 81% yield. $[\alpha]_D$ = +9.31 ($CHCl_3$, c = 0.415, 27°C). 36% ee. [HPLC condition: Chiralcel OD column, n-hexane/2-propanol = 98.5/1.5, 1.0 ml/min, 230 nm UV detector, t= 15.03 min for the isomer in major amount and t = 22.21 min for the isomer in minor amount]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.32-7.30 (m, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.22-7.20 (m, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 2.91-2.83 (m, 2H), 2.22 (s, 1H), 2.14-2.07 (m, 2H), 2.01-1.94 (m, 1H), 1.79-1.74 (m, 1H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 148.9, 142.0, 137.6, 128.9, 128.8, 127.6, 127.4, 126.5, 126.4, 126.3, 75.3, 41.4, 29.8, 18.6.

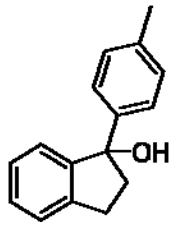



**1-*m*-tolyl-1,2,3,4-tetrahydronaphthalen-1-ol** Colorless oil, 84% yield. $[\alpha]_D$ = 11.71 ($CHCl_3$, c = 0.436, 28°C). 43% ee. [HPLC condition: Chiralcel OD column, n-hexane/2-propanol = 98.5/1.5, 1.0 ml/min, 230 nm UV detector, t= 12.28 min for the isomer in major amount and t = 23.49 min for the isomer in minor amount]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.21-7.13 (m, 4H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.06-7.02 (m, 3H), 2.90-2.82 (m, 2H), 2.32 (s, 3H), 2.17 (s, 1H), 2.14-2.07 (m, 2H), 2.01-1.95 (m, 1H), 1.80-1.75 (m, 1H). $^{13}$C NMR ($CDCl_3$, 150

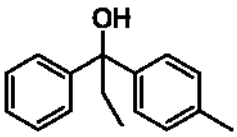
MHz) δ 148.9, 142.0, 137.5, 137.3, 128.9, 128.8, 127.6, 127.4, 127.3, 126.9, 126.4, 123.6, 75.2, 41.4, 29.8, 21.5, 19.6.



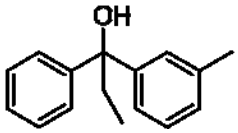

**1-(4-Methoxyphenyl)-1,2,3,4-tetrahydronaphthalen-1-ol** Colorless oil, 84% yield. $[\alpha]_D$ = 13.06 ($CHCl_3$, c = 0.271, 28°C). 49% ee. [HPLC condition: Chiralcel OD column, n-hexane/2-propanol = 98.5/1.5, 1.0 ml/min, 230 nm UV detector, t= 22.96 min for the isomer in major amount and t = 38.97 min for the isomer in minor amount]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.23-7.20 (m, 2H), 7.19-7.18 (m, 1H), 7.15-7.07 (m, 3H), 6.83-6.81 (d, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 2.92-2.83 (m, 2H), 2.17 (s, 1H), 2.14-2.07 (m, 2H), 2.00-1.93 (m, 1H), 1.78-1.72 (m, 1H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 158.2, 142.2, 141.1, 137.5, 128.8(2C), 127.6, 127.4, 126.4, 113.0, 75.1, 55.2, 41.4, 29.8, 19.7.




**1-*p*-Tolyl-2,3-dihydro-1H-inden-1-ol** Colorless oil, 83% yield. $[\alpha]_D$ = -25.01 ($CHCl_3$, c = 0.356, 29°C). 56% ee. [HPLC condition: Chiralcel OD column, n-hexane/2-propanol = 98.5/1.5, 1.0 ml/min, 230 nm UV detector, t= 17.12 min in for the isomer in major amount and t = 25.96 min for the isomer in minor amount].$^1$H NMR ($CDCl_3$, 600 MHz) δ 7.31-7.25 (m, 4H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 2H), 7.08 (d, *J* = 7.8 Hz, 1H), 3.15-3.13 (m, 1H), 2.93-2.89 (m, 1H), 2.49-2.40 (m, 2H), 2.33 (s, 3H), 2.12 (s, 1H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 148.0, 144.0, 143.4, 136.4, 128.7, 128.4, 126.9, 125.6, 124.9, 123.9, 85.3, 47.8, 29.8, 21.0.



**1-Phenyl-1-*p*-tolylpropan-1-ol** 83% yield. $[\alpha]_D$ = -1.41 ($CHCl_3$, c = 0.144, 29°C). 47% ee. [HPLC condition: Chiralcel OD column, n-hexane/2-propanol = 98.5/1.5, 1.0 ml/min, 230 nm UV detector, t= 15.31 min in for the isomer in major amount and t = 16.83 min for the isomer in minor amount]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.40 (d, J = 7.8 Hz, 2H), 7.30-7.28 (m, 4H), 7.20 (t, J = 7.8 Hz, 1H), 7.11 (d, J = 7.8 Hz, 2H), 2.31(s, 3H), 2.29 (q, J = 7.2 Hz, 2H), 2.04 (s, 1H), 0.87 (t, J = 7.2 Hz, 3H).



**1-Phenyl-1-*m*-tolylpropan-1-ol** 83% yield. $[\alpha]_D$ = -1.97 ($CHCl_3$, c = 0.286, 29°C). 39% ee. [HPLC condition: Chiralcel OD column, n-hexane/2-propanol = 98.5/1.5, 1.0 ml/min, 230 nm UV detector, t= 15.31 min in for the isomer in major amount and t = 16.83 min for the isomer in minor amount]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.40 (d, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.24(s, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 5.4 Hz, 2H), 7.03-7.02 (m, 1H), 2.31(s, 3H), 2.29 (q, *J* = 7.2 Hz, 2H), 2.07 (s, 1H), 0.87 (t, *J* = 7.2 Hz, 3H).

# Part II. New Sequential/Tandem Reactions with Transition Metal-Catalyzed Addition Reactions as Part of the Reaction Sequence

# Chapter 5. Aryl Ketone Synthesis via Tandem Orthoplatinated Triarylphosphite-Catalyzed Addition Reactions of Arylboronic Acids with Aldehydes Followed by Oxidation

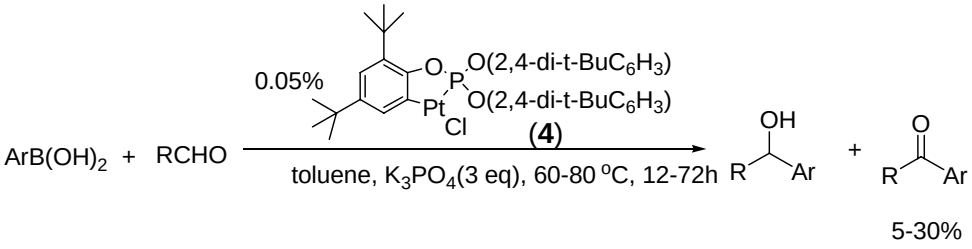
## 5.1 Introduction

Transition-metal-catalyzed addition reactions of organoborons reagents with aldehydes have emerged as useful tools in organic synthesis.[6a,7,10,14b,14e,15b,16,19,27a,28b,31c,32,34a,38,41] In our laboratory, we're interested in employing readily available anionic four-electron donor-based (type I) metalacycles,[30] a large family of cyclic organometallic compounds, as catalysts for such addition reactions.[8-9,21,31a,31c] In previous chapters, we have described type I palladacycle-catalyzed addition reactions of arylboronic acids with carbonyl-containing compounds. We have also employed type I platinacycle **4** as the catalyst for the addition reactions of arylboronic acids with aldehydes. To make these readily available, air-stable type I metalacycles-catalyzed addition reaction more powerful 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.

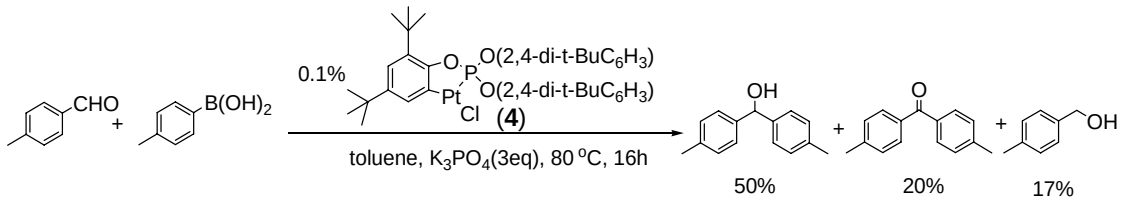
During our research on platinacycle **4**-catalyzed addition reaction of arylboronic acids with aldehydes, we observed some diaryl ketones as byproducts at the amount of 5%-30% while applying extremely low catalyst loading and a large amount of base conditions (Scheme 5.1). Such an observation suggested that aryl ketones were likely formed via the

Oppenauer oxidation of aldehydes with the addition products, that is, some aldehydes played a role of oxidant in catalytic cycle to transform the secondary alcohols to ketones (Scheme 5.2). The oxidation changes to be competitive process while the rate of 1,2-addition reaction significantly decreasing with low catalyst loading. This suggestion illuminated us that if we can identify a simple oxidant to replace the aldehydes for the oxidation of secondary alcohol to ketone, we can likely develop a tandem reaction which combines the 1,2-addition reaction of arylboronic acid with aldehydes and catalytic oxidation reaction of alcohol to ketone into one sequence. In this chapter, we will explore the possibility of combining 1,2-addition reactions with the secondary alcohol oxidation process to access aryl ketones.[42,43]

**Scheme 5.1** Platinacycle **4**-Catalyzed Addition Reaction of Aldehydes with Arylboronic Acids with Arylketones as Byproducts




**Scheme 5.2** Platinacycle **4**-Catalyzed Addition Reaction of *p*-Tolualdehydes with *p*-Tolylboronic Acids




Two groups have recently studied such additions followed by an oxidation reaction sequence.[44] Genet and Darses reported the preparation of diaryl ketones from Rh(I)-catalyzed addition of aldehydes with potassium trifluoro-arylborates[44a,44b] or

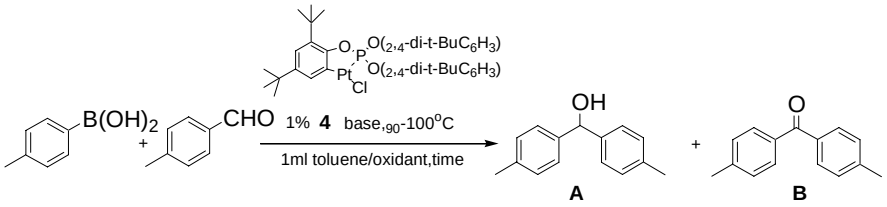
arylboronic acids[44c] followed by an oxidation reaction. Wu reported a one-pot synthesis of diaryl ketones via palladium-catalyzed reaction with arylboronic acids with aldehydes, in which 2 equiv of aldehydes was required.[44d] While these protocols are useful for diaryl ketone synthesis, there are 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, 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.

## 5.2 Tandem Type I Platinacycle-Catalyzed Addition Reaction of Arylboronic Acids with Aldehydes Followed by Oxidation Reaction

We began our study with the identification of a suitable oxidant for the oxidation step for type I platinacycle **4**-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 $^{o}$C in 2 h, the oxidation of the alcohol to ketone was very sluggish and only 3% of ketone was observed (Table 5.1, entries 1 and 2). As acetone has been well-established as an oxidant for

secondary alcohol oxidation,[44a,44b] we seek to use it as the oxidant. We found indeed more ketone product (49%) was formed, which was promising (Table 5.1, 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 5.1, entry 4), 3-pentanone was an excellent oxidant, with almost no aldol condensation between

**Table 5.1** Tandem Platinacycle **4**-Catalyzed Reaction of *p*-Tolualdehyde with *p*-Tolylboronic Acid Followed by Oxidation[a]




| Entry | Oxidant(ml) | Base(equiv) | Conversion[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] |

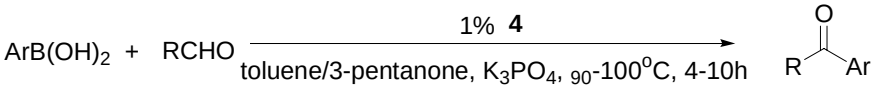
[a]Reaction condition: aldehyde (1.0 eqiuv), *p*-tolylboronic acid (2.0 equiv), solvent and oxidant (1ml), base, 90-100 [o] C. [b] Ratio based on GC/MS. [c] 43% of aldol condensation product from aldehyde with acetone was observed. [d] 13% of aldol condensation product from aldehyde with acetone was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

aldehyde and 3-pentanone being observed (Table 5.1, 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 5.1, 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 5.1, 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 $^oC$ led to a decreasing yield of ketone (Table 5.1, entry 11). Lengthening the reaction time led to more ketone formation (Table 5.1, entry 12).

With 3-pentanone as the oxidant and $K_3PO_4$ as the base, we employed **4** as catalyst for the reactions of different organoboronic acids with various aryl and alkyl aldehydes to explore the applicability of this approach, and our results are listed in Table 5.2. As shown in Table 5.2, good yields were obtained for aromatic aldehydes bearing electron-donating or electron-withdrawing substituents (Table 5.2, 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 aliphatic 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 5.2, entry 22). Since platinacycle **4** could catalyze the addition reaction of arylboronic acids with aldehydes with the catalyst loading of 0.05%, 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 5.2, entry 23). Further lowering the catalyst loading led to a very slow formation of ketone (Table 5.2, entry 24).

**Table 5.2** Orthoplatinated Triaryl Phosphite **4**-Catalyzed Formation of Diaryl Ketones from Aldehydes and Arylboronic Acids[a]




| Entry | Ar-B(OH)$_2$ | RCHO | Yield(%)[b] |
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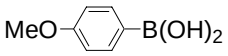
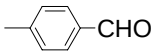
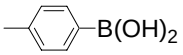
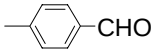
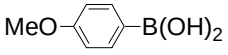
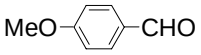
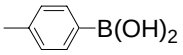
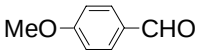
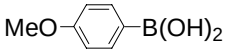
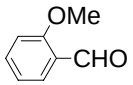
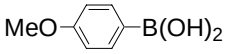
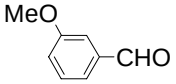
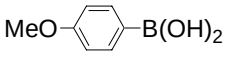
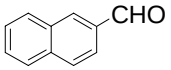
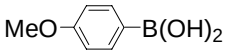
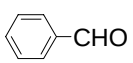
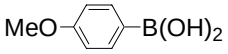
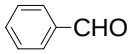
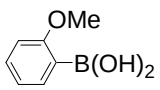
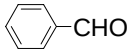
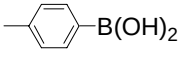
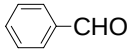
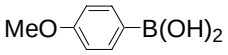
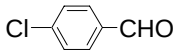
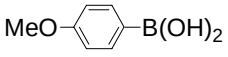
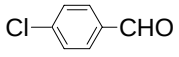
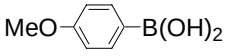
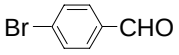
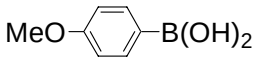
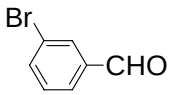
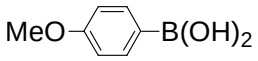
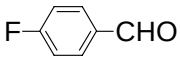
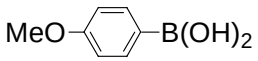
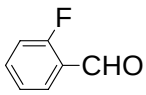
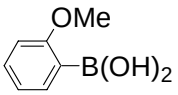
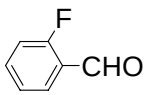
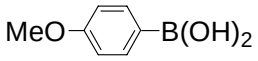
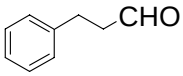
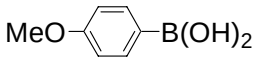
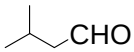
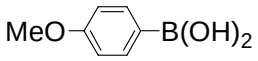
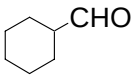
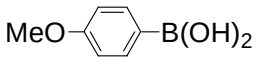
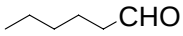
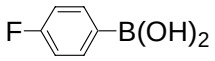
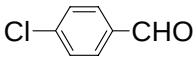
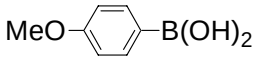
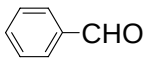
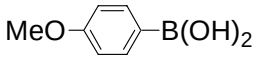
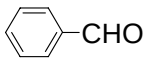
| 1 |  |  | 87 |
| 2 |  |  | 79 |
| 3 |  |  | 82 |
| 4 |  |  | 75 |
| 5 |  |  | 86 |
| 6 |  |  | 81 |
| 7 |  |  | 83 |
| 8 |  |  | 88 |
| 9 |  |  | 84[c] |
| 10 |  |  | 80 |
| 11 |  |  | 81 |
| 12 |  |  | 91 |
| 13 |  |  | 87[c] |
| 14 |  |  | 87 |

**Continued table**

| Entry | Ar-B(OH)$_2$ | RCHO | Yield(%)[b] |
|---|---|---|---|
| 15 |  |  | 82 |
| 16 |  |  | 84 |
| 17 |  |  | 81 |
| 18 |  |  | 70[d] |
| 19 |  |  | 82 |
| 20 |  |  | 71 |
| 21 |  |  | 76 |
| 22 |  |  | 75 |
| 23 |  |  | 27[e] |
| 24 |  |  | 78[f] |
| 25 |  |  | 51[g] |

[a]Reaction conditions: aldehydes (1.0 equiv), arylboronic acid (2.0 eq), **4** (1%), toluene/3-pentanone (4:1/1ml), $K_3PO_4$ (3.0 equiv), 90-100 $^oC$. [b]Isolated yields. [c]1.5 equiv of ArB(OH)$_2$ was used.[d]88%conversion was observation for the oxidation step. [e]88%conversion was observation for theoxidation step.[f]Catalyst loadingis 0.2%. Reaction time:18 h. [g]Catalyst loading: 0.1%. Reaction time: 24 h. 49% of (*p*-methoxyphenyl)-phenylmethanol was observed.

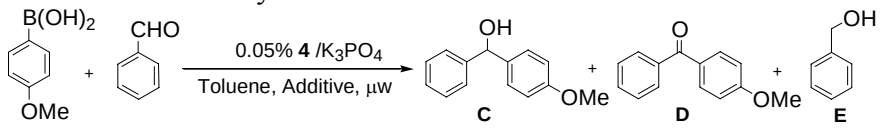
## 5.3 Microwave Irradiation-Assistant Tandem Type I Platinacycle-Catalyzed Addition Reaction of Arylboronic Acids with Aldehydes Followed by Oxidation Reaction

The use of microwave energy to directly heat chemical reactions has blossomed into a useful technique for a variety of applications in organic synthesis and transformations. Heat is created efficiently in the interior of the sample in microwave system compared to the wall heat transfer with conventional heat system, e.g. oil bath.[45] This internal heat transfer results in minimized wall effects (no thermal boundary layer), and thus, microwave heating is a type of very energy efficient heating technique. In addition, temperature for reactions under microwave irradiation could be much higher than that of reactions being heated by conventional methods such as heating in oil bath. Since above advantages, microwave power could provide significant reaction rate and yield enhancements. To further decrease the catalyst loading, we turned our attention to use microwave energy. 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 **4**-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.[31a] We next tested the use of acetone as the oxidant for the reaction. We found while the addition reaction occurred smoothly at 90 $^{o}$C, only 27% of ketone was observed (Table 5.3, 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 $^{o}$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 5.3, entry 6). We next conducted the tandem reaction with ramped temperatures: 90 $^{o}$C for 30 min for the addition reaction and 160 $^{o}$C for 45 min for the oxidation reaction. We found less aldol condensation byproduct was formed (Table 5.3, 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 5.3, entries 7-9).

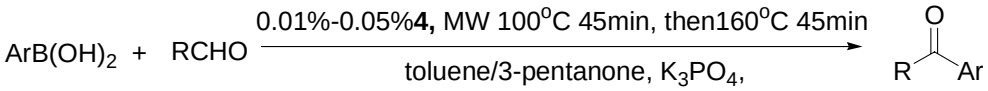
**Table 5.3** Microwave-Assisted, Platinacycle **4**-Catalyzed Addition Reactions of Arylboronic Acids with Aldehydes[a]

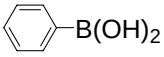
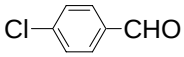
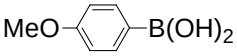
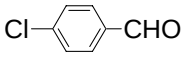
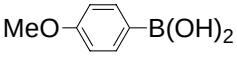
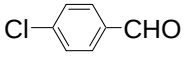
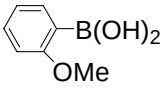
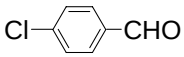
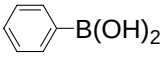
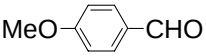
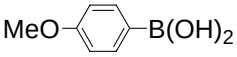
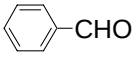
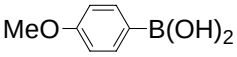
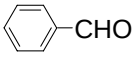
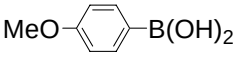
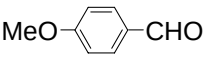
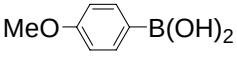
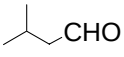
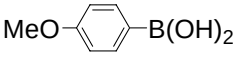
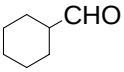
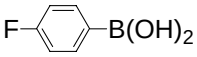
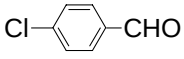
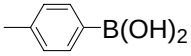
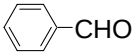
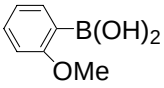
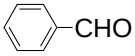
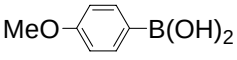
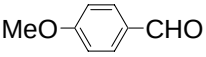
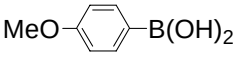
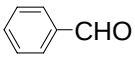
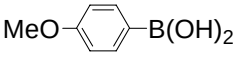
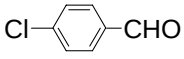



| entry | ***T*** ($^{o}$C), time (min) | additive | Conv[b](%) | ratio of **C/D/E**[c] |
|---|---|---|---|---|
| 1 | 90,30 | | 96 | 96/4/0 |
| 2 | 100, 30 | | 97 | 94/5/1 |
| 3 | 120, 30 | | 97 | 85/9/6 |
| 4 | 140, 30 | | 99 | 74/16/10 |
| 5 | 90, 60 | acetone | 99 | 69/27/0[d] |
| 6 | 160, 60 | acetone | 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 condition: aldehyde (1.0 eqiuv),arylboronic acid (2.0 equiv), **4** (0.05%) toluene (1mL), $K_3PO_4$ (3.0 equiv), microwave(100$^{o}$C, 45 min, 160$^{o}$C, 45 min). [b]Based on $^{1}$H NMR. [c]Based onGC/MS. [d]4% of 4-phenyl-3-buten-2-one was observed.[e]10% of 4-phenyl-3-buten-2-one was observed. [f]5% of 4-phenyl-3-buten-2-one was observed. [g] 4% of 1-phenyl-1-penten-3-one was observed. [h] 2-methyl-1-phenyl-1-penten-3-one was observed.

**Table 5.4** Microwave-Assist Orthoplatinated Triarylphosphite-Catalyzed Tandem Reaction with Aldehydes and Arylboronic Acids by Low Catalyst Loading[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 |
| 12 |  |  | 0.03 | 83[c] |
| 13 |  |  | 0.03 | 86[c] |
| 14 |  |  | 0.01 | 81[c] |
| 15 |  |  | 0.01 | 85[c] |
| 16 |  |  | 0.01 | 88[c] |

[a] Reaction conditions: aldehydes (1.0 equiv), arylboronic acids (2.0 equiv), 4 (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 m bIsolated 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 **4** 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 5.4, entries 1-10) except for 4-fluorophenylboronic acid (Table 5.4, 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 5.4, entries 9-13). Compared to the reported ketone preparation via tandem Rh(I)- and Pd(II)-catalyzed addition reactions followed by oxidation,[44] which required high catalyst loading, limited substrate scope, and/or extra equivalent of aldehydes, our platinacycle **4**-catalyzed tandem addition-oxidation protocols for the synthesis of arylketones competes favorably with these reported methods.

In summary, we have demonstrated that Type I platinacycle **4**-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 **4**-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

## 5.4 Experimental Section

**General**: **General**: NMR spectra were recorded on Varian 300MHz or 600MHz spectrometers. All yields reported refer to isolated yields unless otherwise indicated, and the product purity was estimated to be greater than 95% as determined by $^{1}H$ NMR. Compounds described in the literature were characterized by comparison of their $^{1}H$ NMR and $^{13}C$ NMR spectra to reported data.

All microwave-assisted reactions were conducted in a commercially available microwave reactor, CEM Discover® S-class system, equipped with an infrared temperature detector. The temperatures were controlled within less than ±1–2℃in the temperature-controlled microwave-assisted reaction.

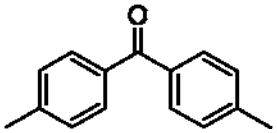
All the thermal heating reaction temperature was conducted in an oil bath with RCT basic IKAMAG® safety control hot plate/magnetic stirrers. The temperature is carefully controlled with a fine temperature controller within ± 1℃.

All the toluene we used was dried and freshly distilled with sodium prior to use. Arylboronic acids were obtained as gifts from Frontier Scientific, Inc. The platinacycle complexes were prepared according to the reported method.[1,2] Other chemical reagents were purchased from Strem Chemicals, Aldrich or Alpha Aesar and used directly.

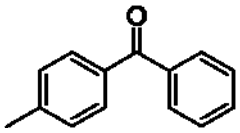
**General procedure for Platinacycle 4-catalyzed addition reactions of arylboronic acids with aldehydes :** To a vial containing aldehyde (0.25 mmol), arylboronic acid (0.5 mmol), $K_3PO_4$ (0.75 mmol) and platinacycle **4** (0.0025mmol) was added toluene (1 ml). After the mixture was stirred at 90-100 $^{o}C$ for 4-8 hours, the reaction was quenched by adding small amount of water. Column chromatography on silica gel with ethyl

acetate/hexane (v/v=1:10) afforded the ketones.

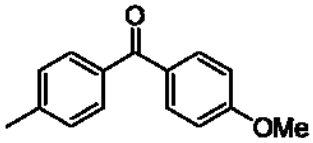
**General procedure for microwave-assisted platinacycle 4-catalyzed addition reactions of arylboronic acids with aldehydes for ketone synthesis:** To a 10-ml pressure vial containing aldehyde (0.50 mmol), arylboronic acid (1.0 mmol), $K_3PO_4$ (0.50 mmol) and platinacycle **4** (0.0025-0.0125mmol) was added toluene (1.6 ml) and 3-pentanone(0.4 ml). After the mixture was irradiated by microwave at 100 $^oC$ for 45 minutes and then ramped to 160 $^oC$ for another 45 minutes, the reaction was quenched by adding small amount of water. Column chromatography on silica gel with ethyl acetate/hexane (v/v=1:10) afforded the alcohols product.



**Di*p*-tolylmethanone** $^1H$ NMR ($CDCl_3$, 600 MHz) δ 7.71 (4H, d, J = 7.8 Hz), 7.28 (6H, t, J = 8.7 Hz), 2.44 (3H, s). $^{13}C$ NMR ($CDCl_3$, 150 MHz) δ 196.29, 142.93, 135.23, 130.20, 128.91, 21.65.

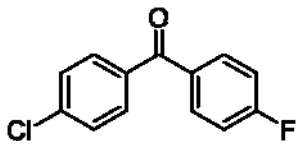


**Phenyl(p-tolyl)methanone** $^1H$ NMR ($CDCl_3$, 600 MHz) δ 7.78 (2H, d, J = 7.8 Hz), 7.72 (2H, d, J = 7.8 Hz), 7.57 (1H, t, J = 7.8 Hz), 7.47 (2H, d, J = 7.2 Hz), 7.28 (2H, d, J = 8.4 Hz), 2.44 (3H, s). $^{13}C$ NMR ($CDCl_3$, 150 MHz) δ 196.46, 143.19, 137.91, 134.83, 132.11, 130.26, 129.88, 128.94, 128.91, 128.16, 21.62.

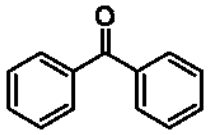



**(4-Methoxyphenyl)(*p*-tolyl)methanone** $^1H$ NMR ($CDCl_3$, 600 MHz) δ 7.81 (2H, d, J = 7.8 Hz), 7.68 (2H, t, J = 7.2 Hz), 7.27

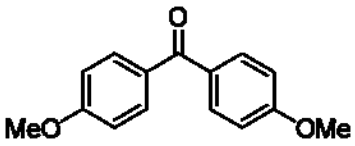
(2H, d, J = 7.8 Hz), 6.96 (2H, d, J = 7.8 Hz), 3.88 (3H, s), 2.43 (3H, s). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 195.30, 162.99, 142.56, 135.47, 132.38, 130.44, 129.96, 128.83, 113.43, 55.44, 21.57.



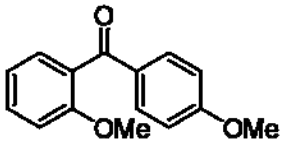

**(4-Chlorophenyl)(4-fluorophenyl)methanone** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.83-7.81 (m, 2H), 7.73 (d, *J*=7.2 Hz, 2H), 7.47 (d, *J*=6.6 Hz, 2H), 7.17 (t, *J*=8.4 Hz, 2H). $^{13}$CNMR ($CDCl_3$, 150 MHz) δ 194.0, 165.5 (d, *J*=253.4 Hz, 1C), 139.0, 135.7, 133.4, 132.5 (d, *J*=9.0 Hz, 1C), 131.3, 128.7, 115.3 (d, *J*=21.8 Hz, 1C). $^{19}$F NMR ($CDCl_3$, 282 MHz) δ -106.1 (1F, s).




**Benzophenone** [2] $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.80 (d, *J*=7.2 Hz, 4H), 7.57 (t, *J*=7.8 Hz, 2H), 7.47 (t, *J*=7.8 Hz, 2H). $^{13}$CNMR ($CDCl_3$, 150 MHz) δ 196.6, 137.5, 132.3, 130.0, 128.2.

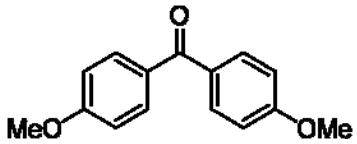



**Bis(4-methoxyphenyl)methanone** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.78 (4H, d, J = 7.2 Hz), 6.96 (4H, d, J = 7.2 Hz), 3.88 (3H, s). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 194.41, 162.79, 132.18, 130.71, 113.41, 55.42.

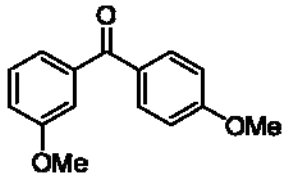



**(2-Methoxyphenyl)(4-methoxyphenyl)methanol** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.81 (2H, d, J = 7.2 Hz), 7.44 (1H, t, J = 7.8 Hz), 7.32 (1H, d, J = 7.8 Hz), 7.03 (1H, t, J = 7.2 Hz), 6.99 (1H, d, J = 7.8 Hz), 3.86 (3H, s), 3.74 (3H, s). $^{13}$C NMR ($CDCl_3$, 150 MHz)

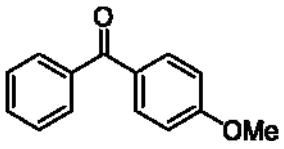
195.04, 163.51, 156.98, 132.25, 131.35, 130.65, 129.25, 129.17, 120.40, 113.44, 111.34, 55.59, 55.42.



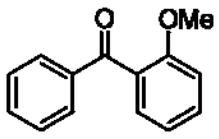

**Bis(4-methoxyphenyl)methanone** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.79 (4H, d, J = 7.2 Hz), 6.96 (4H, d, J = 7.2 Hz), 3.88 (3H, s). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 194.41, 162.80, 132.19, 130.73, 113.42, 55.43




**(3-Methoxyphenyl)(4-methoxyphenyl)methanone** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.85 -7.82 (2H, m), 7.38 -7.35 (1H, m), 7.30 -7.29 (2H, m), 7.11 -7.09 (1H, m), 6.97 -6.94 (2H, m), 3.88 (3H, s), 3.85 (3H, s). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 195.22, 163.18, 159.42, 139.54, 132.48, 130.06, 129.06, 122.32, 118.16, 114.13, 113.47, 55.42, 55.37.

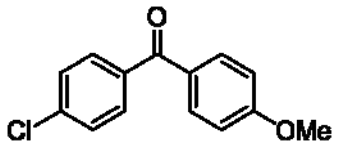



**(4-Methoxyphenyl)(phenyl)methanone** $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.84-7.81 (2H, m), 7.76-7.75 (2H, m), 7.58-7.55 (1H, m), 7.48-7.46 (2H, m), 6.97-6.95 (2H, m), 3.88 (3H, s). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 195.50, 163.17, 138.24, 132.51, 131.84, 130.10, 129.68, 113.50, 55.44.

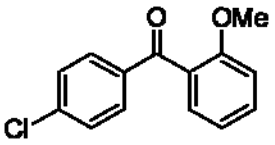



**(2-Methoxyphenyl)(phenyl)methanone** $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.82-7.80 (2H, m), 7.56-7.53 (2H, m), 7.48-7.45 (2H, m), 7.44-7.41 (2H, m), 7.37-7.35 (1H, m), 7.05-7.03 (1H, m), 6.99

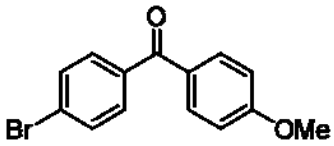
(1H, d, J=8.4 Hz), 3.72 (3H, s). $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 196.43, 157.31, 137.77, 132.88, 131.83, 129.78, 129.54, 128.82, 128.17, 120.45, 111.41, 55.56.



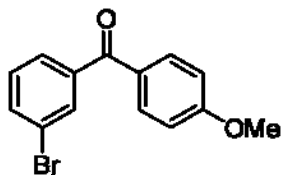

**(4-Chlorophenyl)(4-methoxyphenyl)methanone** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.80-7.79 (2H, m), 7.72-7.70 (2H, m), 7.46-7.44 (2H, m), 6.98-6.96 (2H, m), 3.89 (3H, s). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 194.29, 163.39, 138.28, 136.57, 132.46, 131.16, 129.81, 128.53, 113.59, 55.54.




**(4-Chlorophenyl)(2-methoxyphenyl)methanone** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.74 (2H, d, J=8.4 Hz), 7.48 (1H, dt, J=1.8Hz, J'=8.4 Hz), 7.40 (2H, d, J=8.4 Hz), 7.36 (2H, dd, J=1.8, J'=7.8 Hz), 7.05 (1H, t, J=7.2 Hz), 6.99 (1H, d, J=8.4 Hz), 3.72 (3H, s). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 195.19, 157.25, 139.21, 136.21, 132.19, 131.10, 129.61, 128.49, 128.27, 120.61, 113.39, 55.51.

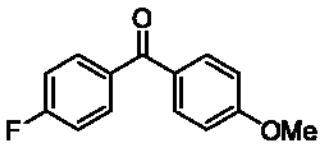



**(4-Bromophenyl)(4-methoxyphenyl)methanone** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.81-7.79 (2H, m), 7.64-7.61 (4H, m), 6.98-6.96 (2H, m), 3.89 (3H, s). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 194.38, 163.40, 136.99, 132.45, 131.48, 131.26, 129.72, 126.81, 113.67, 55.52.

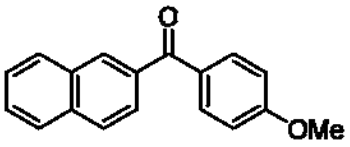



**(3-Bromophenyl)(4-methoxyphenyl)methanone** $^{1}$H NMR

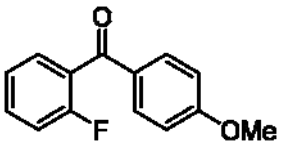
($CDCl_3$, 600 MHz) δ 7.88-7.87 (1H, m), 7.81-7.80 (2H, m), 7.69-7.65 (2H, m), 7.35 (1H, t, J=8.4 Hz), 6.98-6.96 (2H, m), 3.89 (3H, s). $^{13}C$ NMR ($CDCl_3$, 150 MHz) δ 193.79, 163.49, 140.14, 134.68, 132.50, 132.43, 129.74, 129.42, 128.14, 122.40, 113.70, 55.49.



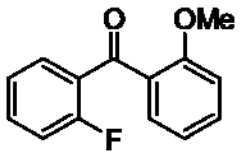

**(4-Fluorophenyl)(4-methoxyphenyl)methanone** $^1H$ NMR ($CDCl_3$, 600 MHz) δ 7.81-7.78 (4H, m), 7.15 (1H, t, J=8.4 Hz), 6.98-6.96 (2H, m), 3.89 (3H, s). $^{13}C$ NMR ($CDCl_3$, 150 MHz) δ 194.05, 165.85, 164.17, 163.22, 134.41, 134.39, 132.36, 132.27, 132.21, 129.97, 115.35, 115.21, 113.59, 55.46. $^{19}F$ NMR ($CDCl_3$, 300 MHz) δ -107.30 (1F, s).



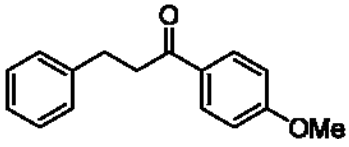

**(4-methoxyphenyl)(naphthalen-2-yl)methanone** $^1H$ NMR ($CDCl_3$, 600 MHz) δ 8.22 (1H, s), 7.93-7.87 (6H, m), 7.60-7.57 (1H, m), 7.55-7.52 (1H, m), 6.99-6.98 (2H, m), 3.89 (3H, s). $^{13}C$ NMR ($CDCl_3$, 150 MHz) δ 195.47, 163.15, 135.44, 134.96, 132.52, 132.21, 131.03, 130.36, 129.20, 128.10, 127.97, 127.74, 126.66, 125.82, 113.55, 55.45.



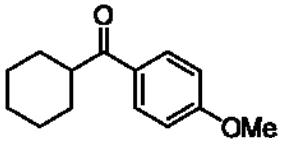

**(2-fluorophenyl)(4-methoxyphenyl)methanone** $^1H$ NMR ($CDCl_3$, 600 MHz) δ 7.84-7.83 (2H, m), 7.52-7.48 (2H, m), 7.27-7.24 (1H, m), 7.15 (1H, t, J = 8.4 Hz), 6.96-6.94 (2H, m), 3.88 (3H, s). $^{13}C$ NMR ($CDCl_3$, 150 MHz) 191.93, 163.90, 160.54, 158.88, 132.52, 132.47, 132.27, 130.44, 130.41, 130.18, 127.52, 127.41, 124.21, 124.19, 116.18, 116.04, 113.71, 55.48. $^{19}F$ NMR ($CDCl_3$, 300 MHz) δ -112.22 (1F, s).



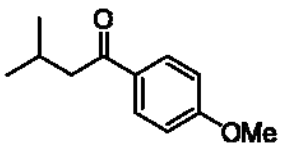

**(2-fluorophenyl)(2-methoxyphenyl)methanone** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.70-7.67 (1H, m), 7.57-7.56 (1H, m), 7.50-7.46 (2H, m), 7.23-7.20 (1H, m), 7.07-7.02 (2H, m), 6.95 (1H, d, J=7.8 ), 3.68 (3H, s). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 192.47, 161.85, 160.16, 158.40, 133.45, 133.39, 133.26, 130.81, 130.80, 130.32, 129.40, 128.42, 128.34, 123.98, 123.96, 120.58, 110.90, 115.76, 111.47, 55.57. $^{19}$F NMR ($CDCl_3$, 300 MHz) δ -112.67 (1F, s).



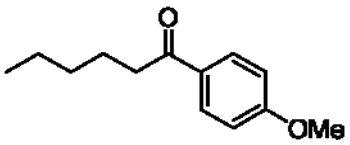

**1-(4-Methoxyphenyl)-3-phenylpropan-1-one** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.96-7.93 (2H, m), 7.3 (2H, t，J=7.2 Hz), 7.26-7.25 (2H, m), 7.20 (1H, t, J=7.2 Hz), 6.93-6.91 (2H, m), 3.86 (3H, s), 3.26-3.24 (2H, m), 3.06 (2H, t, J=7.8 Hz). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 197.80, 163.42, 141.45, 130.29, 129.95, 128.49, 128.41, 126.06, 113.70, 55.45, 40.11, 30.31.




**Cyclohexyl(4-methoxyphenyl)methanone** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.95-7.93 (2H, m), 6.95-6.93 (2H, m), 3.87 (3H, s), 3.25-3.20 (1H, m), 1.88-1.83 (4H, m), 1.76-1.72 (1H, m), 1.54-1.47 (2H, m), 1.43-1.35 (2H, m), 1.31-1.23 (2H, m),. $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 202.44, 163.18, 130.48, 129.25, 113.67, 55.41, 45.29, 29.53, 25.96, 25.90.




**1-(4-Methoxyphenyl)-3-methylbutan-1-one** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.95-7.93 (2H, m), 6.94-6.92 (2H, m), 3.87 (3H, s), 2.78 (2H, d, J=7.2 Hz), 2.31-2.25 (1H, m), 0.99 (6H, d, J=6.6 Hz). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 198.86, 163.27, 130.50, 130.35, 113.62, 55.41, 47.17, 25.36, 22.77.




**1-(4-Methoxyphenyl)hexan-1-one** $^{1}$H NMR ($CDCl_3$, 600 MHz) δ 7.95 (2H, d, J= 9.0 Hz), 6.93 (2H, d, J= 8.4 Hz), 3.86 (3H, s), 2.90 (2H, t, J=7.8 Hz), 1.74-1.71 (2H, m), 1.37-1.34 (4H, m) 0.92-0.91 (3H, m). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 199.21, 163.25, 130.27, 130.16, 113.61, 55.40, 38.23, 31.58, 24.29, 22.51, 13.93.

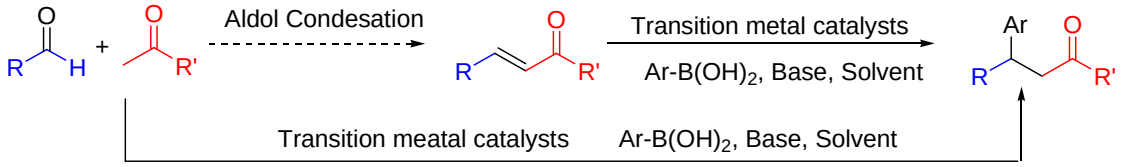
# Chapter 6. Sequential/Tandem Aldol Condensation – Transition Metal-Catalyzed Addition Reactions of Aldehydes, Methyl Ketones and Arylboronic Acids

## 6.1 Introduction

Transition metal-catalyzed addition reactions of arylboronic acids with carbonyl-containing compounds and derivatives have recently emerged as useful transformations for organic synthesis in part due to the nature of low toxicity and air/moisture stability of arylboronic acids.[14b,14e,27a,27c] One of the most noteworthy achievements in this field might be transition metal-catalyzed addition reaction of arylboronic acids with α,β-unsaturated ketones, which yield synthetically useful β-substituted ketones as the products.[27c,28b,46] While good to high enantioselectivities have been achieved for this type of addition reaction, the prepurified α, β-unsaturated ketones were used. Although α, β-unsaturated ketones can be "readily" obtained from the aldol condensation of aldehydes and/or ketones, the use of prepurified α, β-unsaturated ketones apparently posed some limits: they require an extra purification/separation step from aldehydes/ketones and are less available than aldehydes/ketones. During our study on transition metal-catalyzed addition reactions of arylboronic acids with carbonyl-containing compounds,[8,15b,31a,37,47] we became interested in combining such transition metal-catalyzed addition reactions with the formation of α,β-unsaturated ketones in a sequential or tandem fashion.[48] We reasoned that achieving such sequential/tandem reactions would minimize the effort for the preparation of α,β-unsaturated ketones because prepurification for such ketones is eliminated, and may also expand the

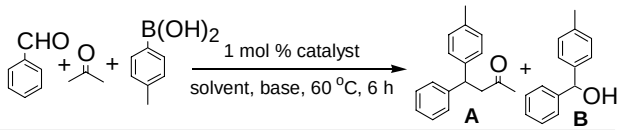
α,β-unsaturated ketone substrate scope.

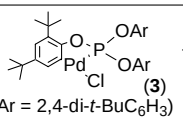
**Scheme 6.1** Preparation of β-Arylated Ketones




We tested the possibility of combining the aldol condensation with addition reaction into one sequence. We mixed benzaldehyde, acetone and *p*-tolylboronic acid together with palladacycle **3** or $[Rh(COD)Cl]_2$ as the catalyst. We found with toluene or THF-MeOH as the solvent, the desired reaction product (A) was the minor product and the major product was the 1,2-addition product (B) (Table 6.1). We speculated that this reaction outcome was likely due to the fact that transition metal-catalyzed addition of *p*-tolylboronic acid with benzaldehyde occurred faster than the aldol condensation of benzaldehyde with acetone under the reaction condition.

**Table 6.1** Tandem Aldol Condensation-Transition Metal-Catalyzed Reaction of Benzaldehyde, Acetone and *p*-Tolylboronic Acid [a]




| entry | catalyst | solvent | base | conv (%) [b] | A/B [b] |
|---|---|---|---|---|---|
| 1 |  (**3**) (Ar = 2,4-di-*t*-BuC$_6$H$_3$) | Toluene | $K_3PO_4$ | 99 | 1:99 |
| 2 | **3** | Toluene | $K_3PO_4$ | 63 [c] | 12:88 |
| 3 | $[Rh(COD)Cl]_2$ | Toluene | $K_3PO_4$ | 30 | 1:99 |
| 4 | **3** | THF-MeOH | $K_2CO_3$ | 24 [d] | 1:99 [e] |
| 5 | $[Rh(COD)Cl]_2$ | THF-MeOH | $K_2CO_3$ | 87 [d] | 1:99 [f] |

a. Reaction condition: benzaldehyde (0.25 mmol), acetone (0.3 mL), *p*-tolylboronic acid (2.0 equiv), toluene (0.7 mL) or THF/MeOH (1.0 mL/0.1 mL), base (3.0 equiv), 60 °C. b. Based on GC-MS analysis. c. 2.0 equiv of $H_2O$ were added to the reaction system. d. 22 equiv of $H_2O$ were added to the reaction system. e.14% of phenyl *p*-tolyl ketone was observed. f. 9% of phenyl *p*-tolyl ketone was observed.

There are two strategies to overcome the fast 1,2-addition reaction issue. One strategy is carrying out the reaction of aldehydes, methyl ketones and arylboronic acids in a sequential fashion: the arylboronic acids and the catalyst were introduced into the reaction system after the completion of the aldol condensation. Another strategy is slowing down the 1,2-addition reaction significantly. This may be realized by choosing less active catalysts for addition reactions or protonic solvents which are demonstrated to be effective for retarding the 1,2-addition reactions but still usable for 1,4-addition reactions. Following this strategy, we could have a chance to achieve the reaction of aldehydes, methyl ketones and arylboronic acids to prepare β-arylated ketones in a tandem fashion which are operationally more convenient than sequential reactions. In this chapter, I will report a full description of developments on synthesis of β-arylated ketones via aldol condensation of aldehydes with methyl ketones followed by transition metal-catalyzed addition reaction from sequential sequence to tandem sequence.

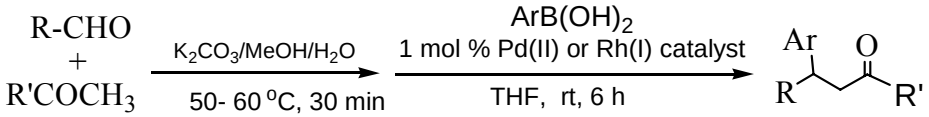
## 6.2 Sequential Aldol Condensation–Transition Metal-Catalyzed Addition Reactions of Aldehydes, Methyl Ketones and Arylboronic Acids

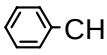
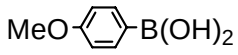
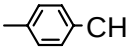
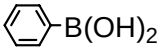
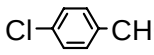
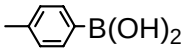
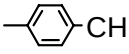
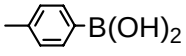
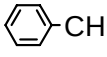
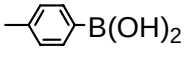
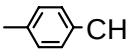
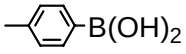
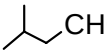
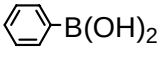
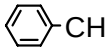
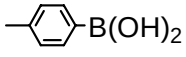
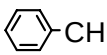
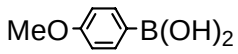
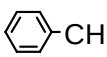
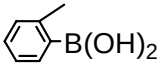
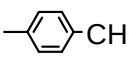
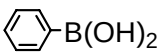
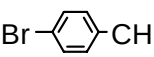
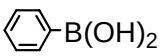
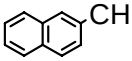
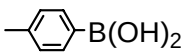
To overcome the fast 1,2-addition reaction issue, we examined the first strategy and carried out the reaction of aldehydes, methyl ketones and arylboronic acids in a sequential fashion: the arylboronic acids, and the catalyst were introduced into the reaction system after the completion of the aldol condensation. We found with $K_2CO_3$ as the base, THF/MeOH as the solvent and palladacycle **3** or $[Rh(COD)Cl]_2$ as catalyst of 1,4-addition reaction, the sequential reactions of acetone, aldehydes and arylboronic acids occurred smoothly at room temperature (Table 6.2, entries 1-3, 8-13). We also tested

2-butanone, 2-pentanone, acetophenone and 3-pentanone for the reaction. We found that 2-butanone, 2-pentanone and acetophenone were suitable ketones (Table 6.2, entries 4-5, 7 and 14-18). On the other hand, we also found that 3-pentanone was inefficient for the sequential reaction (Table 6.2, entry 6), likely because the aldol condensation between benzaldehyde and 3-pentanone occurred too slowly. We also found aliphatic aldehydes, which can also undergo aldol reactions with themselves, were suitable starting materials for the new sequential reaction (Table 6.2, entries 7, 18).

We next turned our attention to the asymmetric version of this sequential β-aryl ketone formation process. We selected Rh(I) complexes for our study because Rh(I)/chiral ligand-catalyzed 1,4-addition reactions of arylboronic acids with α,β-unsaturated ketones have been established. We examined four optically active ligands, **11**,[49] **12**,[50] 1,1'-spirobiindane-7,7'-diol (SPINOL)-based phosphite **13**[10h,51] and **14**,[18a] that were available to us and our results are listed in Table 3. We found while Rh(I)/ligand **12** and Rh(I)/ligand **14** were poor catalysts for the sequential aldol condensation-addition reaction (Table 6.3, entries 2, 4), Rh(I)/(*R*)-BINAP **11** and Rh(I)/ligand **13** exhibited good catalytic activities and enantioselectivities (Table 6.3, entries 1, 3). Other factors that could influence the enantioselectivity of the reaction were then examined. We found that with **13** as the ligand**,** $K_2CO_3$ as the base and THF as the solvent, the enantioselectivity could be improved to 89% (Table 6.3, entries 6- 11). Decreasing the reaction temperature from room temperature to 0 $^{o}$C further improved the enantioselectivity to 92% (Table 6.3, entry 12).

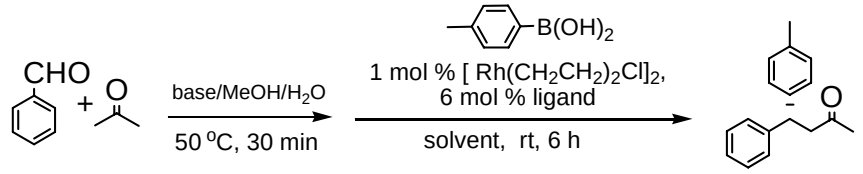
**Table 6.2** Sequential Aldol Condensation-Transition Metal-Catalyzed Addition Reactions of Aldehydes, Methyl Ketones and Arylboronic Acids [a]

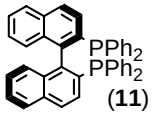
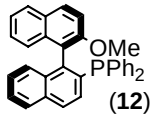
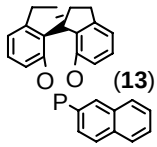
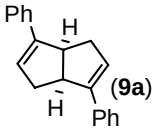



| entry | catalyst | RCHO | $R'COCH_3$ | $Ar'B(OH)_2$ | yield(%) [b] |
|---|---|---|---|---|---|
| 1 | **3** |  |  |  | 84 |
| 2 | **3** |  |  |  | 87 |
| 3 | **3** |  |  |  | 88 |
| 4 | **3** |  |  |  | 86 |
| 5 | **3** |  |  |  | 74 |
| 6 | **3** |  |  |  | 0 [c] |
| 7 | **3** |  |  |  | 65 |
| 8 | $[Rh(COD)Cl]_2$ |  |  |  | 81 [d] |
| 9 | $[Rh(COD)Cl]_2$ |  |  |  | 82 |
| 10 | $[Rh(COD)Cl]_2$ |  |  |  | 85 |
| 11 | $[Rh(COD)Cl]_2$ |  |  |  | 89 |
| 12 | $[Rh(COD)Cl]_2$ |  |  |  | 86 |
| 13 | $[Rh(COD)Cl]_2$ |  |  |  | 84 |
| 14 | $[Rh(COD)Cl]_2$ |  |  |  | 86 |
| 15 | $[Rh(COD)Cl]_2$ |  |  |  | 85 |
| 16 | $[Rh(COD)Cl]_2$ |  |  |  | 81 |
| 17 | $[Rh(COD)Cl]_2$ |  |  |  | 84 |
| 18 | $[Rh(COD)Cl]_2$ |  |  |  | 82 |

a. Reaction condition: aldehyde (0.25 mmol,1.0 equiv), acetone (0.1 mL), $H_2O$ ( 0.1 mL) and $K_2CO_3$ (1.0 equiv), 50 °C for 30 min, then **3** or $[Rh(COD)Cl]_2$ (1 mol %), THF (1 mL) and arylboronic acids (0.5 mmol, 2.0 equiv) were added into the mixture at rt for another 6 h. b. Isolated yield. c. 16% of 1-Phenyl-2-methyl-1-penten-3-one was observed. d. The reaction was carried out in 2.5 mmol scale.

**Table 6.3** Asymmetric Sequential Aldol Condensation-Rh(I)/Ligand-Catalyzed Addition Reaction of Benzaldehyde, Acetone and *p*-Tolylboronic Acid [a]



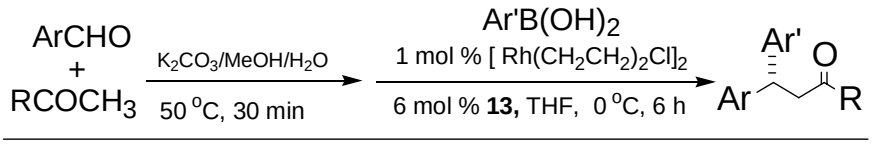

| entry | ligand | base | temp. | solvent | yield (%) [b] | ee (%) [c] |
|---|---|---|---|---|---|---|
| 1 |  (**11**) | KOH | 100 °C | Toluene | 82 | 81 |
| 2 |  (**12**) | KOH | rt | Toluene | 10 | — |
| 3 |  (**13**) | KOH | rt | Toluene | 81 | 79 |
| 4 |  (**9a**) | KOH | rt | Toluene | 30 | — |
| 5 | **11** | $K_2CO_3$ | rt | THF | 80 | 80 |
| 6 | **13** | $K_2CO_3$ | rt | THF | 83 | 89 |
| 7 | **13** | $K_2CO_3$ | rt | THF | 81 [d] | 88 |
| 8 | **13** | $K_2CO_3$ | rt | Toluene | 78 | 81 |
| 9 | **13** | $K_3PO_4$ | rt | Toluene | 70 | 53 |
| 10 | **13** | $Cs_2CO_3$ | rt | Toluene | 81 | 75 |
| 11 | **13** | $K_2CO_3$ | rt | 1,4-dioxane | 76 | 83 |
| 12 | **13** | $K_2CO_3$ | 0 °C | THF | 84 [e] | 92 |

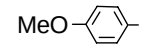
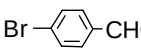
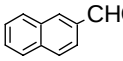
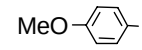
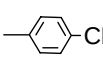
a. Reaction condition: benzaldehyde (0.25 mmol,1.0 eqiuv), *p*-tolylboronic acid (2.0 equiv), solvent (1 mL), acetone (0.2 mL), $H_2O$ (0.1 mL), base (1.0 equiv). b. Isolated yield. c. Determined by HPLC (Chiralcel OD Column). d. 4 mol % **13** was used. e. Reaction temperature: 0 °C.

Several aldehydes, methyl ketones and arylboronic acids were examined for the asymmetric sequential aldol condensation-Rh(I)/**13**-catalyzed addition reaction. Optically active β-arylated ketones were obtained in good yields and good enantioselectivity (Table 6.4, entries 1-8). Because this sequential reaction involved α,β-unsaturated ketones, generated from the aldol condensation of aldehydes and methyl ketones, and arylboronic

acids, we reasoned that optically active β-arylated ketones with opposite chiral configurations could be obtained with the same Rh(I)/**13** catalyst by simply reversing the aryl groups on aldehydes and arylboronic acids. We found indeed that (*R*)-4-phenyl-4-*p*-tolylbutan-2-one, generated from benzaldehyde, acetone and *p*-tolylboronic acid, and (*S*)-4-phenyl-4-*p*-tolylbutan-2-one, generated from *p*-tolualdehyde, acetone and phenylboronic acid, were obtained in excellent enantioselectivity with the same Rh(I)/**13** catalyst (Table 6.4, entries 1, 9).

**Table 6.4**. Asymmetric Sequential Aldol Condensation-Rh(I)-Catalyzed Addition Reactions of Aldehydes, Methyl Ketones and Arylboronic Acids [a]




| entry | ArCHO |  | $Ar'B(OH)_2$ | yield (%) [b] | ee (%) [c] |
|---|---|---|---|---|---|
| 1 |  |  |  | 84 | 92 (*R*) [d] |
| 2 |  |  |  | 80 | 87 (*R*) [d] |
| 3 |  |  |  | 87 | 82 |
| 4 |  |  |  | 87 | 83 |
| 5 |  |  |  | 85 | 86 |
| 6 |  |  |  | 81 | 87 |
| 7 |  |  |  | 80 | 82 |
| 8 |  |  |  | 83 | 86 |
| 9 |  |  |  | 86 | 91 (*S*) |

a. Reaction condition: aldehyde (0.25 mmol,1.0 equiv), arylboronic acid (2.0 equiv), MeOH (0.1 mL), ketone (0.2 mL), $H_2O$( 0.1 mL), $K_2CO_3$ (3.0 equiv), 0 °C. b. Isolated yield. c. Determined by HPLC analysis( Chiral OD Column). d. Established by comparision of the HPLC data with reported ones.

In this work, we demonstrated that the aldol condensation of aldehydes with methyl ketones followed by transition metal-catalyzed addition reactions with arylboronic acids could occur efficiently in a sequential fashion, affording various β-arylated ketones. By using an optically active 1,1'-spirobiindane-7,7'-diol (SPINOL)-based phosphite as the ligand, a Rh(I)-catalyzed asymmetric version of such a sequential reaction has been realized and up to 92% ee was achieved. This study provided an efficient method to access β-substituted ketones from readily available aldehydes with methyl ketones, and arylboronic acids might lead to the development of other new sequential/tandem reactions with transition metal-catalyzed addition reactions as part of the reaction.

## 6.3 Tandem Aldol Condensation – Platinacycle-Catalyzed Addition Reactions of Aldehydes, Methyl Ketones and Arylboronic Acids

Although this sequential methodology is advanced for its fast access β-substituted ketones from readily available substrates, the inconveniences like adding substrates and changing reaction condition during the reaction process make us be interested in developing such reaction in a tandem fashion which are operationally more convenient than sequential reactions as reaction materials are loaded altogether at the beginning. In the following section, I will describe the results of studies on preparation of β-substituted ketones from readily available aldehydes with methyl ketones, and arylboronic acids through a tandem fashion.

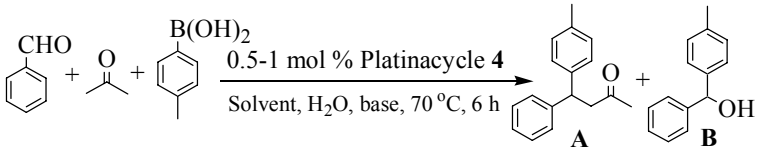
Based on our previous study that Type I platinacycle **4**[12] (Figure 1)-catalyzed 1,2-addition reaction of aldehydes with arylboronic acids occurred slower than that with

Type I palladacycles as catalysts,[3a] we surmised that it might be possible to realized the reaction of aldehydes, methyl ketones and arylboronic acids in a tandem fashion by using platinacycle **4** as the 1,4-addition reaction catalyst.[3a,11c]

Our study began with the condition screening for the tandem aldol condensation reaction of benzaldehyde with acetone followed by platinacycle **4**-catalyzed additions of *p*-tolylboronic acid. Toluene was chosen as the solvent and $K_3PO_4$ as the base for our study because they were identified as the best solvent and base in platinacycle **4**-catalyzed addition reactions of arylboronic acids with aldehydes.[3a] As a temperature of 80 $^oC$ or higher was needed for platinacycle **4**-catalyzed addition reactions of arylboronic acids with aldehydes to occur efficiently,[3a] we reasoned that carrying out the tandem reaction at a temperature of lower than 80 $^oC$ might suppress the 1,2-addition reaction of arylboronic acids with aldehydes. We thus began our study at 70 $^oC$. We found although the desired tandem reaction product was observed to be only 31% of the reaction mixture, the moderate reaction conversion (31%) suggested that the platinacycle **4**–catalyzed addition reaction of *p*-tolylboronic acid with benzaldehyde indeed occurred very slowly (Table 6.5, entry 1). We speculated that the moderate conversion might be because the first step, the aldol condensation reaction step, occurred very slowly. As $K_3PO_4$ is insoluble in toluene, we reasoned that the presence of water might facilitate the aldol condensation reaction, and the tandem reaction process. We thus tested to use water as the additive and found indeed the existence of a small amount of water significantly facilitated the tandem reaction (Table 6.5, entries 1-3). By using 7 equivalents of water as the additive, the tandem aldol condensation followed by platinacycle **4**-catalyzed addition reaction occurred efficiently, afford the β-arylated ketone as the major product (Table 6.5,

entry 4). Further testing of other bases revealed that $K_2CO_3$, $Cs_2CO_3$ and KOH were more effective bases than $K_3PO_4$ for the tandem reaction. By using these bases, excellent conversions were observed, with the tandem aldol condensation-addition reaction product as the predominant product (Table 6.5, entries 6, 8, 10).

**Table 6.5**. Tandem Aldol Condensation-Transition Metal-Catalyzed Reaction of Benzaldehyde, Acetone and Phenylboronic Acid [a]



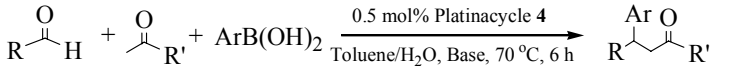

| Entry | Solvent | $H_2O$ (equiv) | Base | Conv. [b] | **A**/**B** [b] |
|---|---|---|---|---|---|
| 1 | Toluene | 0 | $K_3PO_4$ | 31% | 31:64 |
| 2 | Toluene | 2 | $K_3PO_4$ | 52% | 65:35 |
| 3 | Toluene | 4 | $K_3PO_4$ | 69% | 77:23 |
| 4 | Toluene | 7 | $K_3PO_4$ | 73% | 92:8 |
| 5 | Toluene | 4 | $K_2CO_3$ | 72% | 80:20 |
| 6 | Toluene | 7 | $K_2CO_3$ | 95% | 99:1 |
| 7 | Toluene | 4 | $Cs_2CO_3$ | 87% | 97:3 |
| 8 | Toulene | 4 | $Cs_2CO_3$ | 94% [c] | 99:1 |
| 9 | THF | 4 | $Cs_2CO_3$ | 67% | 99:1 |
| 10 | Toluene | 7 | KOH | 99% [d] | 99:1 |

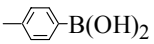
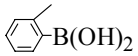
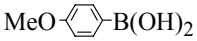
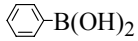
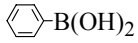
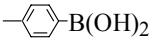
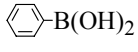
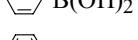
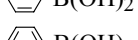
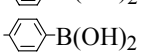
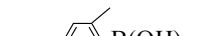
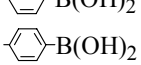
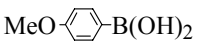
a. Reaction condition: aldehyde (1.0 eqiuv), *p*-toluboronic acid (2.0 equiv), solvent (0.7 mL), acetone (0.3 mL), base (3.0 equiv), 70 °C. b. Based on GC-MS analysis. c.15% of 1,5-diphenyl-1,5-di(*p*-tolyl)-3-pentanone was observed. d. 5% of 1,5-diphenyl-1,5-di(*p*-tolyl)-3-pentanone was observed.

After identifying the reaction condition, the scope of the tandem aldol condensation followed by Type I platinacycle **4**-catalyzed addition reaction was examined. Different aromatic aldehydes, methyl ketones and arylboronic acids were suitable starting materials for the tandem reaction and high yields were observed for all cases being tested (Table 6.6). The combination of aromatic aldehydes, methyl ketones and arylboronic acids permitted the access of a variety of β-aryl ketones including β-aryl ketones that have not been reported before, mainly because of the availability of such α,β-unsaturated ketones

(Table 6.6).

**Table 6.6** Tandem Aldol Condensation-Platinacycle **4**-Catalyzed Reaction of Aromatic Aldehydes, Methyl Ketones and Arylboronic Acids [a]




| Entry | RCHO | $R'COCH_3$ | $ArB(OH)_2$ | Base | Yield(%)[b] |
|---|---|---|---|---|---|
| 1 |  |  |  | $K_2CO_3$ | 86 |
| 2 |  |  |  | $K_2CO_3$ | 84 |
| 3 |  |  |  | $K_2CO_3$ | 81 |
| 4 |  |  |  | $K_2CO_3$ | 86 |
| 5 |  |  |  | $K_2CO_3$ | 87 |
| 6 |  |  |  | $K_2CO_3$ | 85 |
| 7 |  |  |  | $K_2CO_3$ | 86 |
| 8 |  |  |  | $K_2CO_3$ | 86 |
| 9 |  |  |  | KOH | 85 |
| 10 |  |  |  | KOH | 83 |
| 11 |  |  |  | KOH | 91 |
| 12 |  |  |  | KOH | 80 |
| 13 |  |  |  | KOH | 86 |
| 14 |  |  |  | KOH | 85 |
| 15 |  |  |  | KOH | 87 |
| 16 |  |  |  | KOH | 82 [c] |
| 17 |  |  |  | KOH | 84 [c] |
| 18 |  |  |  | KOH | 82 [c] |
| 19 |  |  |  | KOH | 91 [c] |
| 20 |  |  |  | KOH | 88 [c] |
| 21 |  |  |  | $Cs_2CO_3$ | 70 |
| 22 |  |  |  | $Cs_2CO_3$ | 76 |

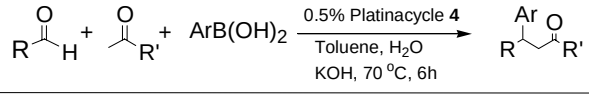
a. Reaction condition: aldehyde (0.25 mmol, 1.0 equiv), arylboronic acid (2.0 equiv), toluene (0.8 mL), ketone (0.2 mL), $H_2O$ (7 equiv), base (3.0 equiv), 70 °C.

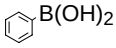
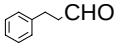
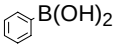
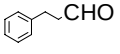
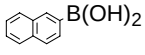
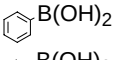
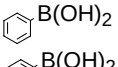
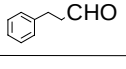
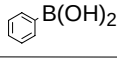
b. Isolated yield. c. $H_2O$ (13 equiv) was used.

We next examined aliphatic aldehydes as the aldehyde source for the tandem reaction, which could lead the formation of β-alkyl-β-aryl ketones. Aliphatic aldehydes are

considered to be more problematic aldehydes than aromatic aldehydes for the tandem reaction because they may undergo a self-aldol condensation reaction under the reaction condition. Such possible self-aldol condensation reaction of aldehydes rendered β-alkyl α,β-unsaturated ketones much less available than β-aryl α,β-unsaturated ketones. We were particularly interested in accessing β-alkyl-β-aryl ketones that have not been reported before by using transition metal-catalyzed addition reactions, mainly because of the availability of their precursors, β-alkyl α,β-unsaturated ketones. We found aliphatic aldehydes were suitable starting materials, with the β-alkyl-β-aryl ketones being obtained in good yields (Table 6.7), and the self-aldol condensation reaction was negligible. Thus, although β-alkyl α,β-unsaturated ketones are less available due to the self-aldol condensation of aliphatic aldehydes, our study provided an efficient route to a variety of β-alkyl-β-aryl ketones from readily available methyl ketones, aliphatic aldehydes and arylboronic acids.

**Table 6.7** Tandem Aldol Condensation-Platinacycle **4**-Catalyzed Reaction of Aliphatic Aldehydes, Methyl Ketones and Arylboronic Acids [a]

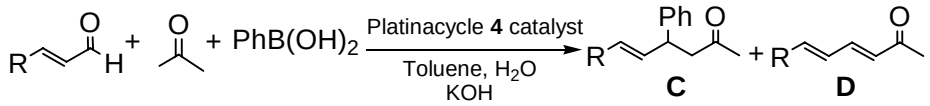



| Entry | RCHO | $RCOCH_3$ | $ArB(OH)_2$ | Yield(%)[b] |
|---|---|---|---|---|
| 1 |  |  |  | 80 |
| 2 |  |  |  | 76 |
| 3 |  |  |  | 74 |
| 4 |  |  |  | 77 |
| 5 |  |  |  | 83 |
| 6 |  |  |  | 80 |
| 7 |  |  |  | 78 |

a. Reaction condition: aldehyde (1.0 eqiuv), arylboronic acid (2.0 equiv), ketone (0.2 mL), toluene (0.8 mL), $H_2O$ (0.1 mL), KOH (3.0 equiv), 70 °C.
b. Isolated yield .

α,β-Unsaturated aldehydes were also examined as the aldehyde source for the tandem reaction (Table 6.8). We found that by using KOH as the base, the tandem aldol condensation followed by 1,4-addition reaction occurred, but the reaction could not reach a complete conversion for the aldol condensation reaction products. A significant amount of the aldol condensation reaction product was observed even after lengthening the reaction time, increasing the amount of phenylboronic acid, or raising the reaction temperature. Such an observation might suggest that the δ,γ-double bond of the dienone likely served as a ligand to stabilize the Pt species after the 1,4-addition reaction of arylboronic acid with the dienone, which might hinder the regeneration of the Pt catalyst for the tandem reaction.

**Table 6.8** Tandem Aldol Condensation-Platinacycle **4**-Catalyzed Reaction of α,β-Unsaturated Aldehydes, Acetone and Phenylboronic Acid [a]




| Entry | R | Cat. Loading | Temp.(°C) | Time. | **C** : **D** | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | Ph | 1 mol % | 70 | 8 h | 60 : 40 | - |
| 2 | Ph | 1 mol % | 70 | 16 h | 60 : 40 | - |
| 3 | Ph | 2 mol % | 80 | 8 h | 75: 25 | - |
| 4 | Ph | 2 mol % | 70 | 8 h | 75 : 25 [c] | 68 |
| 5 | $CH_3$ | 2 mol % | 80 | 10 h | 50 : 50 [d] | - |

a. Reaction condition: aldehyde (1.0 eqiuv), arylboronic acid (2.0 equiv), toluene (0.8 mL), acetone (0.2 mL), $H_2O$ (13 equiv.), KOH (3.0 equiv), 70 °C. b. Isolated yield of **C**. c. 4 Equiv of $PhB(OH)_2$ was used. d. 2,4,7,9-Undecatetraen-6-one was observed as the aldol condensation product.

In this work, we have demonstrated that platinacycle **4**-catalyzed addition reactions of arylboronic acids with α,β-unsaturated ketones can be combined with the formation of α,β-unsaturated ketones, the aldol condensation reaction of aromatic and aliphatic

aldehydes with methyl ketones, in a tandem fashion efficiently. A variety of β-arylated ketones can be obtained in good to high yields from readily available aromatic/aliphatic aldehydes, methyl ketones and arylboronic acids. Our future work will be directed to develop asymmetric version of such tandem reactions and other tandem/sequential reactions involving the addition reaction of arylboronic acids with aldehydes as part of the reaction sequence.

## 6.4 Tandem Aldol Condensation–Rhodium Complexes-Catalyzed Addition Reactions of Aldehydes, Methyl Ketones and Arylboronic Acids

Although we can successfully prepare β-arylated ketones via tandem aldol condensation–platinacycle-catalyzed addition reactions of aldehydes, methyl ketones and arylboronic acids, the chiral version of this tandem synthesis is still unsuccessful for lack of suitable chiral platinum complexes. We thus turn our attention back to employ Rh(I) complexes as the catalyst of the addition reaction since the catalytic activity and enantioselectivity of the catalyst systems could be readily altered by using a number of readily available ligands.

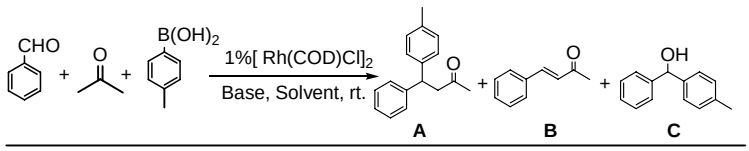
In the second section, we documented that $[Rh(COD)Cl]_2$ was a good catalyst for the preparation of β-arylated ketones via sequential aldol condensation-transition metal-catalyzed addition reactions of aldehydes, methyl ketones and arylboronic acids. However, $[Rh(COD)Cl]_2$ could not be employed in the tandem fashion because $[Rh(COD)Cl]_2$-catalyzed addition of arylboronic acids with aldehydes occurred faster than the aldol condensation of aldehydes with methyl ketones under those reaction conditions. To achieve that aldol condensations-Rh(I) complexes-catalyzed addition

reactions occur smoothly in a tandem fashion, one possible strategy is to increase the reaction rate of the aldol condensation reaction and/or retard the transition metal-catalyzed 1,2-addition reactions. It is known that Rh(I)-catalyzed 1,2-addition reactions of arylboronic acids with aldehydes could be retarded significantly but 1,4-addition of arylboronic acids with α,β-unsaturated carbonyl-containing compounds still occurred smoothly with protonic solvents like methanol and water was employed. It is well-established that stronger base can accelerate the rate of aldol condensation reaction of aldehydes and methyl ketones. We surmised that it is possible to realize the reaction of aldehydes, methyl ketones and arylboronic acids in a tandem fashion by using Rh(I) complexes as the 1,4-addition reaction catalysts, methanol/$H_2O$ as solvent and KOH as base. We thus have an opportunity to develop asymmetric version of such a tandem reaction.

Our study began with the condition screening for the tandem aldol condensation of benzaldehyde with acetone followed by $[Rh(COD)Cl]_2$-catalyzed additions of *p*-tolylboronic acid, methanol/water/tetrahedrofuran mixed with varied ratios as the solvent for our study because methanol and water were identified as the best solvent for aldol condensation of aldehydes with methyl ketones and tetrahydrofuran was a suitable solvent in Rh(I)-catalyzed addition reactions of arylboronic acids with α,β-unsaturated ketones based on our sequential reaction conditions. Although the 1,2-addition reaction of benzaldehydes with *p*-tolylboronic acid occurred prior to the aldol condensation of benzaldehydes with acetone while $K_2CO_3$ served as base, the strong base like KOH can significantly improve the rate of aldol condensation reaction (Table 6.9, entries 1-2) and gave a promising conversion of β-arylated ketone. We found that the 1,2-addition

reaction of benzaldehyde with *p*-tolylboronic acid was sluggish when methanol was the main component of mixed solvents (table 6.9, entry 3-7). β-arylated ketone can be exclusively achieved while the reaction occurred with Methanol/$H_2O$/THF in the volume ratio of 5:1:2 as the mixed solvent and KOH as base at room temperature for 24 hours (Table 6.9, entry 4). Further experiments revealed that a certain amount of THF is necessary for this tandem reaction which may help in situ generated α,β-unsaturated ketone to be soluble in the reaction system (Table 6.9, entry 5). We found the reaction time can be shortened to 3 hours while the amount of phenylboronic acid decreased to 1.5 equivalents, which suggested that most of KOH was consumed by phenylboronic acid while 2 equivalents of phenylboronic acid was used.

**Table 6.9** Tandem Aldol Condensation-$[Rh(COD)Cl]_2$-Catalyzed Reaction of Benzaldehyde, Acetone and *p*-Tolylboronic Acid [a]



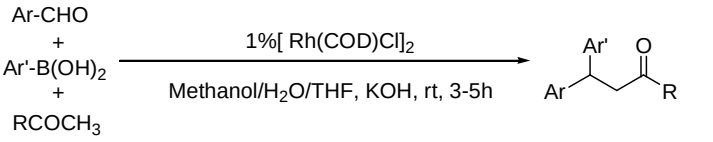

| entry | base(equiv) | MeOH/$H_2O$/THF | time(h) | **A/B/C** |
|---|---|---|---|---|
| 1 | $K_2CO_3$(3) | 0.1mL/0.1mL/0.6mL | 13 | 0/1/99 |
| 2 | KOH(3) | 0.1mL/0.1mL/0.6mL | 13 | 64/17/19 |
| 3 | KOH(3) | 0.5mL/0.1mL/0.2mL | 13 | 75/24/1 |
| 4 | KOH(3) | 0.5mL/0.1mL/0.2mL | 24 | 99/0/1 |
| 5 | KOH(3) | 0.7mL/0.1mL/0mL | 13 | 38/15/47 |
| 6[c] | KOH(3) | 0.5mL/0.1mL/0.2mL | 3 | 99/0/1 |
| 7[c] | KOH(4) | 0.5mL/0.1mL/0.2mL | 3 | 99/0/1 |

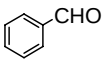
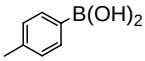
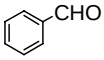
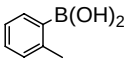
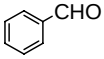
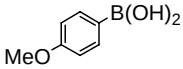
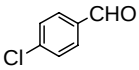
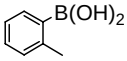
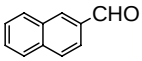
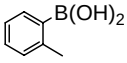
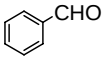
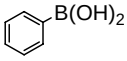
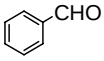
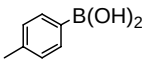
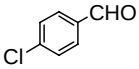
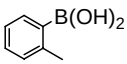
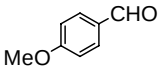
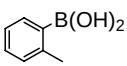
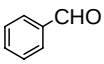
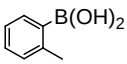
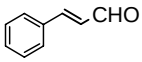
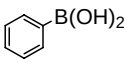
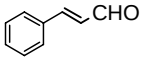
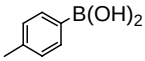
a. Reaction condition: aldehyde (1.0 equiv), p-toluboronic acid (2.0 equiv), solvent (0.8 ml), acetone (0.3 mL), base (3-4 eqive), rt. b. Based on GC-MS analysis. c.*p*-toluboronic acid (1.5 equiv)

After identifying the reaction conditions, the scope of the tandem aldol condensation followed by $[Rh(COD)Cl]_2$-catalyzed addition reaction was examined. Different aromatic aldehydes, methyl ketones and arylboronic acids were suitable starting materials for the

tandem reaction and high yields were observed for all cases being tested (Table 6.10). α,β-Unsaturated aldehydes were also suitable aldehyde source for the tandem reaction and good yields were observed for all case being tested.

**Table 6.10** Tandem Aldol Condensation-$[Rh(COD)Cl]_2$-Catalyzed Reaction of Aromatic Aldehydes, Methyl Ketones and Arylboronic Acids [a]



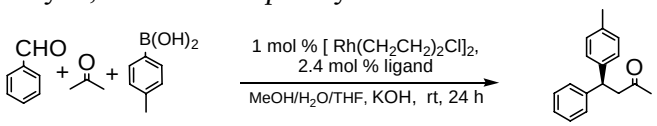

| Entry | Ar-CHO | $RCOCH_3$ | $Ar'-B(OH)_2$ | Yield(%)[b] |
|---|---|---|---|---|
| 1 |  |  |  | 91 |
| 2 |  |  |  | 89 |
| 3 |  |  |  | 86 |
| 4 |  |  |  | 90 |
| 5 |  |  |  | 85 |
| 6 |  |  |  | 88[c] |
| 7 |  |  |  | 87[c] |
| 8 |  |  |  | 86[c] |
| 9 |  |  |  | 84[c] |
| 10 |  |  |  | 82 |
| 11 |  |  |  | 81 |
| 12 |  |  |  | 83 |

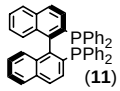
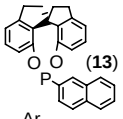
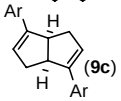
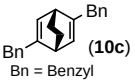
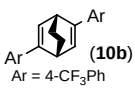
a. Reaction condition: aldehyde (1.0 equiv), *p*-toluboronic acid (1.5 equiv), Methanol/ $H_2O$/THF(0.5 mL/0.1mL/0.2mL), ketone (0.2 mL), KOH (3 eqive), rt. 3-5 h; b. Isolated yield; c. 4 equiv KOH.

We next turned our attention to the asymmetric version of this tandem β-aryl ketone formation process. We selected Rh(I) complexes for our study because Rh(I)/chiral

ligand-catalyzed 1,4-addition reactions of arylboronic acids with α,β-unsaturated ketones have been established.[1,3] We examined four optically active ligands, (*R*)-BINAP **11**, 1,1'-spirobiindane-7,7'-diol (SPINOL)-based phosphite **13**, tetrahydropentalenes **9c** and [2.2.2]-bicyclooctadiene **10c** and **10b**, those were available to us and our results are listed in Table 6.11. We found while Rh(I)/ligand **3** was poor catalysts for the tandem aldol condensation-addition reaction (Table 6.11, entries 3), Rh(I)/(*R*)-BINAP **11**, Rh(I)/ligand **13** and Rh(I)/ [2.2.2]-bicyclooctadienes **10c** and **10b** exhibited attractive catalytic activities and enantioselectivities (Table 6.11, entries 1-2, 4-6). We found that with Rh(I)/ligand **10b** as the catalyst**,** MeOH/$H_2O$/THF(V/V/V=5:1:2) as the solvent, the best enantioselectivity and yield could be achieved at 92% and 92% respectively (Table 6.11, entries 6).

**Table 6.11** Asymmetric Tandeml Aldol Condensation-Rh(I)/Ligand-Catalyzed Addition Reaction of Benzaldehyde, Acetone and *p*-Tolylboronic Acid [a]



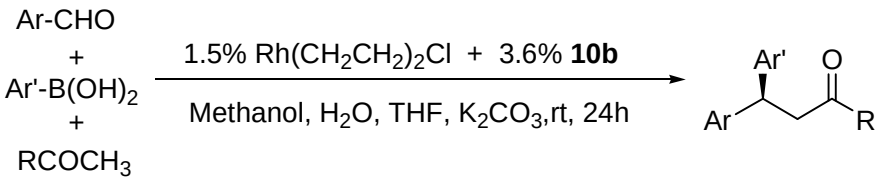

| entry | ligand | MeOH/$H_2O$/THF | yield (%) [b] | ee (%) [c] |
|---|---|---|---|---|
| 1 |  (**11**) | MeOH/$H_2O$/THF 0.1mL/0.1mL/0.5mL | 67 | 80[d] |
| 2 |  (**13**) | MeOH/$H_2O$/THF 0.1mL/0.1mL/0.5mL | 52 | 86[d] |
| 3 |  (**9c**) Ar = 4-$CF_3$Ph | MeOH/$H_2O$/THF 0.1mL/0.1mL/0.5mL | 22[e] | — |
| 4 |  (**10c**) Bn = Benzyl | MeOH/$H_2O$/THF 0.1mL/0.1mL/0.5mL | 85 | 91 |
| 5 |  (**10b**) Ar = 4-$CF_3$Ph | MeOH/$H_2O$/THF 0.1mL/0.1mL/0.5mL | 90 | 92 |
| 6 | (**10b**) | MeOH/$H_2O$/THF 0.5mL/0.1mL/0.2mL | 92 | 92 |

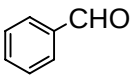
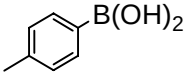
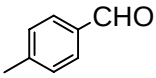
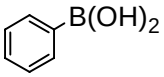
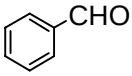
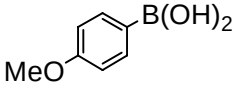
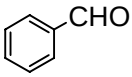
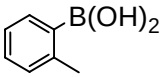
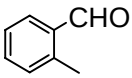
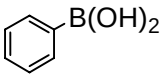
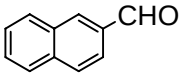
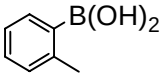
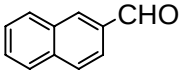
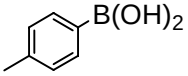
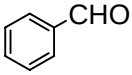
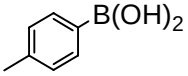
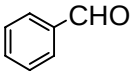
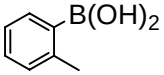
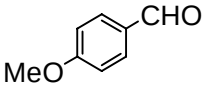
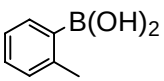
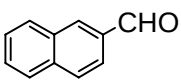
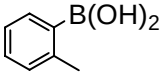
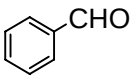
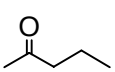
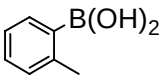
a. Reaction condition: benzaldehyde (0.25 mmol,1.0 eqiuv), *p*-tolylboronic acid (1.5 equiv), acetone (0.2 mL), $H_2O$ (0.1 mL), KOH (3.0 equiv). b. Isolated yield. c. determined by HPLC (Chiralcel OD Column). d. 4 mol % ligand was used. e. Conversion based on GC/MS.

Several aldehydes, methyl ketones and arylboronic acids were examined for the asymmetric tandem aldol condensation-Rh(I)/**10b**-catalyzed addition reaction. Optically active β-arylated ketones were obtained in good yields and excellent to good enantioselectivity (Table 6.12, entries 1-8).

In this work, we demonstrated that the aldol condensation of aldehydes with methyl ketones followed by $[Rh(COD)Cl]_2$-catalyzed addition reactions with arylboronic acids could occur efficiently in a tandem fashion, affording various β-arylated ketones. By using an optically active [2.2.2]-bicyclooctadienes as the ligand, a Rh(I)-catalyzed asymmetric version of such a tandem reaction has been realized and up to 99% ee was achieved. This study provided an efficient method to access β-substituted ketones from readily available aldehydes with methyl ketones, and arylboronic acids and might lead to the development of other new sequential/tandem reactions with transition metal-catalyzed addition reactions as part of the reaction.

**Table 6.12** Asymmetric Tandem Aldol Condensation-Rh(I)-Catalyzed Addition Reactions of Aldehydes, Methyl Ketones and Arylboronic Acids [a]




| Entry | Ar-CHO | $RCOCH_3$ | Ar'-$B(OH)_2$ | Yield(%)[b] | e.e.(%)[c] |
|---|---|---|---|---|---|
| 1 |  |  |  | 90 | 92(S) |
| 2 |  |  |  | 84 | 83(R) |
| 3 |  |  |  | 81 | 93(R) |
| 4 |  |  |  | 89 | 98 |
| 5 |  |  |  | 83 | 84 |
| 6 |  |  |  | 86 | 96 |
| 7 |  |  |  | 84 | 92 |
| 8 |  |  |  | 87 | 93 |
| 9 |  |  |  | 86 | 99 |
| 10 |  |  |  | 81 | 99 |
| 11 |  |  |  | 84 | 98 |
| 12 |  |  |  | 82 | 96 |

a. Reaction condition: aldehyde (0.25 mmol,1.0 eqiuv), arylboronic acid (1.5 equiv), Methanol/$H_2O$/THF (0.5mL/ 0.1mL/ 0.2mL), ketone (0.2 mL), KOH (3.0 equiv).
b. Isolated yield. c. Determined by HPLC (Chiralcel OD Column).

## 6.5 Summary

In this chapter, we reported a full description of developments on synthesis of β-arylated ketones via aldol condensation of aldehydes with methyl ketones followed by transition metal-catalyzed addition reaction in sequential and tandem fashion. To overcome the fast 1,2-addition reaction of aldehydes with arylboronic acids issue, we carried out this aldol condensation followed by addition reaction in a sequential fashion. The asymmetric version of this sequential reaction has also been realized by using an optically active Rh(I)/1,1'-spirobiindane-7,7'-diol (SPINOL)-based phosphite as a catalyst and up to 92% enantioselectivity was achieved. By using stronger bases and less active platinacycle as addition reaction catalyst, the 1,2-addition reaction occurred much slower than aldol condensation, we developed those aldol condensation of aldehydes with methyl ketones followed by platinacycle-catalyzed addition reaction in tandem fashion. The 1,2-addition reaction was retarded significantly by using protonic solvents. Under the strong base condition, aldol condensation of aldehydes with methyl ketones followed by $[Rh(COD)Cl]_2$-catalyzed addition reaction can occur in tandem fashion. We then developed such tandem reaction in asymmetric version. Good to excellent (up to 99%) enantioselectivity were achieved with Rh(I)/[2.2.2]- bicyclooctadiene as catalyst.

This study provided an efficient method to access β-substituted ketones from readily available aldehydes, methyl ketones and arylboronic acids. It might lead to the development of other new sequential/tandem reactions with transition metal-catalyzed addition reactions as part of the reaction.

Our future work will be continued to develop double aldol condensation of aldehydes and acetone followed by transition metal-catalyzed double 1,4-addition reaction in

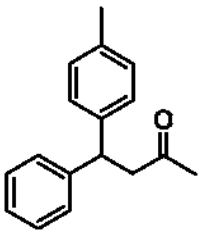
sequential/tandem fashion including asymmetric version.

## 6.6 Experimental Section

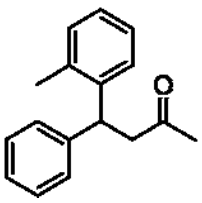
**General**: NMR spectra were recorded on Varian 300MHz or 600MHz spectrometers. Elemental analysis was carried out by Altantic Microanalysis, Inc., Norcross, GA. High resolution mass spectra(HRMS) were acquired by Agilent G6520 Q-TOF mass spectrometer. All yields reported refer to isolated yields unless otherwise indicated, and the product purity was estimated to be greater than 95% as determined by $^{1}$H NMR. Compounds described in the literature were characterized by comparison of their 1H NMR and $^{13}$C NMR spectra to reported data. New compounds were also characterized by element analysis or high resolution mass. Arylboronic acids were obtained as gifts from Frontier Scientific, Inc. Palladacycle **1** was prepared according to the reported method.1 Other chemical reagents were purchased from Strem Chemicals, Aldrich or Alpha Aesar and used directly.

**General procedure for sequential aldol condensation-transition metal-catalyzed addition reactions of aldehydes, methyl ketones and arylboronic acids:** In a glove-box, to a vial containing aldehyde (0.25 mmol) and $K_2CO_3$ (0.75 mmol) were added ketone (0.2 mL), methanol (0.1 mL) and water (0.1 mL). After the mixture was stirred at 50 - 60 $^{o}$C for 30 min, arylboronic acid (0.5 mmol), THF (1 mL) and $[Rh(COD)Cl]_2$ or palladacycle **3** (0.0025 mmol) (An Ohaus Explorer analytic balance with 0.1 mg accuracy was used for weighing the catalysts) were added into reaction mixture and then stirred at room temperature for another 6 hours. The reaction was

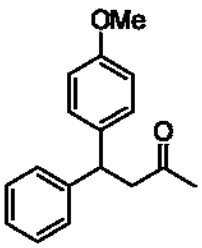
quenched by adding 4 N HCl (2 mL) aqueous solution. The mixture was extracted with $CH_2Cl_2$ (3 x15 mL). The organic layers were combined. After evaporation of the organic solvents, the residue was subjected to column chromatography [silica gel, ethyl acetate/hexane (v/v=1:20) as eluent] to afford the products.



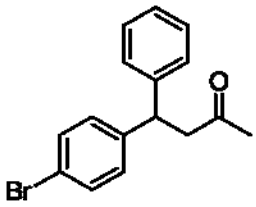
**4-Phenyl-4-*p*-tolylbutan-2-one** $^1$H NMR ($CDCl_3$, 600 MHz)： δ 7.27-7.24 (m, 2H), 7.21-7.20 (m, 2H), 7.17-7.14 (m, 1H), 7.11-7.06 (m, 4H), 4.57 (t, *J*=7.2 Hz, 1H), 3.13 (d, *J*=7.2 Hz, 2H), 2.28 (s, 3H), 2.06 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 206.9, 144.0, 140.7, 135.9, 129.2, 128.5, 127.6, 127.5, 126.3, 49.7, 45.6, 30.6, 20.9 ppm.



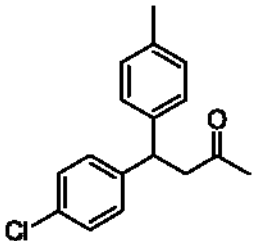
**4-Phenyl-4-*o*-tolylbutan-2-one** $^1$H NMR ($CDCl_3$, 600 MHz): δ 7.25-7.22 (m, 4H), 7.17-7.12 (m, 5H), 4.78 (t, *J*=7.2 Hz, 1H), 3.14 (d, *J*=7.2 Hz, 2H), 2.29 (s, 3H), 2.06 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 206.8, 143.5, 141.5, 136.3, 130.8, 128.4, 127.9, 126.40, 126.2 (2C), 126.0, 50.0, 41.9, 30.6, 19.8 ppm.



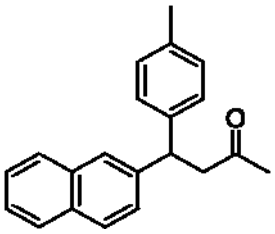
**4-(4-Methoxyphenyl)-4-phenylbutan-2-one** $^1$H NMR ($CDCl_3$, 600 MHz): δ 7.26 (t, *J*=7.2 Hz, 4H), 7.21-7.19 (m, 2H), 7.17-7.12 (m, 3H), 6.82-6.79(m, 2H), 4.53 (t, *J*=7.2 Hz, 1H), 3.70 (s, 3H,), 3.14 (d, *J*=7.8 Hz, 1H), 2.06 (3H, s) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 207.0, 158.0, 144.2, 135.9, 128.6, 128.5, 127.5, 126.3, 113.9, 55.2, 49.8, 45.2, 30.6 ppm.



**4-(4-Bromophenyl)-4-phenylbutan-2-one** Light yellow oil. $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.38 (d, *J*=7.8 Hz, 2H), 7.27 (t, *J*=7.8 Hz, 2H), 7.18-7.17 (m, 3H), 7.09 (d, *J*=8.4 Hz, 2H), 4.55 (t, *J*=7.2 Hz, 1H), 3.15 (d, *J*=7.2 Hz, 1H), 2.07 (3H, s) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 206.3, 143.2, 142.9, 131.6, 129.4, 128.6, 127.5, 126.6, 120.2, 49.3, 45.3, 30.6 ppm. IR (neat): 3060(w), 3027(w), 2969(w), 2897(w), 1717(s), 1487(s), 699(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{16}H_{19}BrNO$ $[M+NH_4]^+$ 322.0626, found 322.0626.

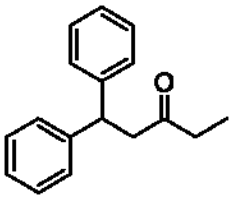


**4-(4-Chlorophenyl)-4-p-tolylbutan-2-one** White solid, m.p. 70-71°C. $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.24 (d, *J*=8.4 Hz, 2H), 7.15 (d, *J*=8.4 Hz, 2H), 7.08 (m, 4H), 4.53 (t, *J*=7.2 Hz, 1H), 3.14 (d, *J*=7.2 Hz, 2H), 2.30 (s, 3H), 2.09 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): 206.5, 142.6 140.3, 136.2, 132.1, 129.4, 129.0, 128.7, 127.4, 126.3, 49.7, 45.6, 30.6, 20.9 ppm. IR (neat) υ 3030(w), 3001(w), 2920(m), 1704(s), 1490(s), 1349(s), 762(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{17}H_{18}ClO$ $[M+H]^+$ 273.1041, found 273.1043.

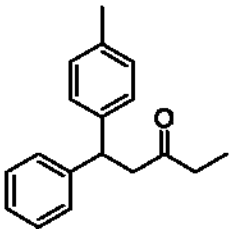


**4-(Naphthalen-2-yl)-4-p-tolylbutan-2-one** Pale yellow solid, m.p.79-80°C.$^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.77 (t, *J*=7.8 Hz, 2H), 7.73 (d, *J*=8.4 Hz, 1H), 7.67 (m, 4H), 7.45-7.40 (m, 2H), 7.31 (d, *J*=8.4 Hz, 1H), 7.15-7.03 (m, 4H), 4.71 (t, *J*=7.2 Hz, 1H), 3.25 (t, *J*=7.8 Hz, 2H), 2.28 (s, 3H), 2.09 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 206.9, 141.5, 140.7, 136.0, 133.4, 132.2, 129.3, 128.3, 127.7 (2C), 127.5, 126.5, 126.0,

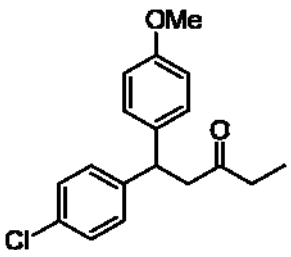
125.6, 125.5, 49.6, 45.7, 30.7, 20.9 ppm. IR (neat) 3025(w), 2968(m), 1710(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{21}H_{24}NO$ $[M+NH_4]^+$ 306.1852, found 306.1854.



**1,1-Diphenylpentan-3-one** White solid, m.p.26-27°C. $^1H$ NMR ($CDCl_3$, 600 MHz): δ 7.27-7.25 (m, 4H), 7.22-7.21 (m, 4H), 7.18-7.15 (m, 2H), 4.61 (t, J=7.2 Hz, 1H), 3.14 (d, J=7.2 Hz, 2H), 2.32 (q, J=7.2 Hz, 2H), 0.94 (t, J=7.2 Hz, 3H) ppm. $^{13}C$ NMR ($CDCl_3$, 150 MHz): δ 209. 5, 143.9, 128.5, 127.7, 126.4, 48.4, 46.0, 36.7, 7.5 ppm. IR (neat) 3028(w), 2940(w), 1710(m), 1494(m), 1452(m), 697(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{17}H_{22}NO$ $[M+NH_4]^+$ 256.1696, found 256.1697.

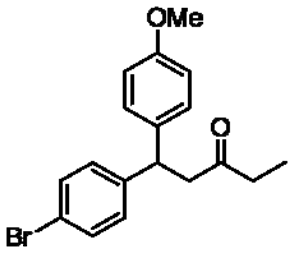


**1-Phenyl-1-p-tolylpentan-3-one** White solid, m.p. 28-29°C.$^1H$ NMR ($CDCl_3$, 600 MHz): δ 7.27-7.24 (m, 2H), 7.20-7.19 (m, 2H), 7.17-7.14 (m, 1H), 7.11-7.07 (m, 4H), 4.54 (t, J=7.2 Hz, 1H), 3.15 (d, J=7.2 Hz, 2H), 2.33 (q, J=7.2 Hz, 2H), 2.28 (s, 3H), 0.95 (t, J=7.2 Hz, 3H) ppm. $^{13}C$ NMR ($CDCl_3$, 150 MHz): δ 209.6, 144.2 141.0, 129.2, 128.5, 127.7, 127.6, 126.3, 48.6, 45.7, 36.7, 21.0, 7.6 ppm. IR (neat) 3025(w), 2921(m), 1711(s), 1514(m), 1454(m), 773(m), 726(s), 699(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{18}H_{20}NaO$ $[M+Na]^+$ 275.1406, found 275.1409.



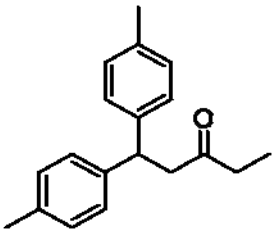

**1-(4-Chlorophenyl)-1-(4-methoxyphenyl)pentan-3-one** White solid, m.p. 50°C. $^1H$ NMR ($CDCl_3$, 600 MHz): δ 7.23 (d, J=8.4 Hz, 2H), 7.14 (d, J=8.4 Hz, 2H), 7.10 (d, J=8.4 Hz,

2H), 6.82 (d, J=8.4 Hz, 2H), 4.54 (t, J=7.2 Hz, 1H), 3.76 (s, 3H), 3.10 (d, J=7.8 Hz, 2H), 2.34 (q, J=7.2 Hz, 2H), 0.96 (t, J=7.8 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 209.2, 158.2, 142.9, 135.6, 132.0, 129.0 (2C), 128.5, 114.0, 55.2, 48.4, 44.5, 36.7, 7.5 ppm. IR (neat) 2974(w), 2940(w), 2884(m), 1708(s), 1464(s), 818(s) $cm^{-1}$.Anal. Calcd for $C_{18}H_{19}ClO_2$: C, 71.40; H, 6.32; Found: C, 71.47; H, 6.32.



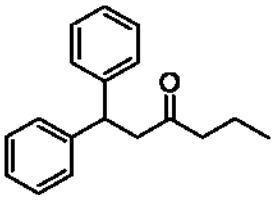

**1-(4-Bromophenyl)-1-(4-methoxyphenyl)pentan-3-one**

Colorless oil. $^1$H NMR ($CDCl_3$, 600 MHz): δ 7.38 (d, *J*=9.0 Hz, 2H), 7.10 (d, *J*=8.4 Hz, 2H), 7.08 (d, *J*=8.4 Hz, 2H), 6.82-6.81 (m, 2H), 4.52 (t, J=7.2 Hz, 1H), 3.76 (s, 3H), 3.09 (d, *J*=7.8 Hz, 2H), 2.34 (q, *J*=7.2 Hz, 2H), 0.96 (t, *J*=7.2 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 209.2, 158.2, 143.4, 135.5, 131.5, 129.3, 128.5, 120.1, 114.0, 55.2, 48.4, 44.6, 36.7, 7.5 ppm. IR (neat) υ 2972(w), 2936(w), 2903(w), 2835(w), 1714(s), 1511(s), 1248(s) $cm^{-1}$. Anal. Calcd for $C_{18}H_{19}BrO_2$: C, 62.26; H, 5.52; Found: C, 62.10; H, 5.46.

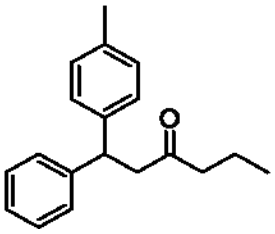



**1,1-Di*p*-tolylpentan-3-one** White solid, m.p. 83-84$^o$C. $^1$H NMR ($CDCl_3$, 600 MHz): δ 7.10-7.05 (m, 8H), 4.53 (t, *J*=7.8 Hz, 1H), 3.76 (s, 3H), 3.11 (d, *J*=7.2 Hz, 2H), 2.32 (q, *J*=7.2 Hz, 2H), 2.78 (s, 6H), 0.96 (t, *J*=7.2 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 209.7, 141.2, 135.8, 129.2, 127.5, 48.6, 45.3, 36.7, 20.9, 7.5 ppm. IR (neat) 2980(m), 2923(m), 1712(s), 1512(m), 1373(m), 1108(s), 805(s) $cm^{-1}$. Anal. Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.32; Found: C, 85.51; H,

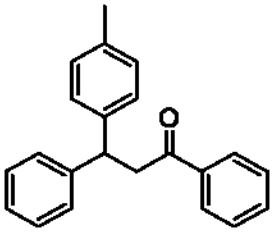
8.34.



**1,1-Diphenylhexan-3-one** Light yellow oil. $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.27-7.14 (m, 10H), 4.61 (t, *J*=7.8 Hz, 1H), 3.13 (d, *J*=7.2 Hz, 2H), 2.30-2.27 (m, 2H), 1.53-1.46 (m, 2H), 0.79 (t, *J*=7.2 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 208.9, 143.9, 128.5, 127.7, 126.3, 48.7, 45.9, 45.4, 16.9, 13.5 ppm. IR (neat) 3061(w), 3028(w), 2961(w), 2874(w), 1712(m), 698(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{18}H_{20}NaO$ $[M+Na]^+$ 275.1406, found 275.1408.

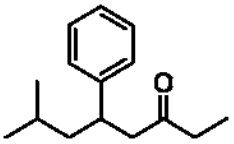


**1-Phenyl-1-p-tolylhexan-3-one** Light yellow oil. $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.24 (t, *J*=7.8 Hz, 3H), 7.21-7.19 (m, 2H), 7.14 (t, *J*=7.2 Hz, 3H), 7.10 (d, *J*=8.4 Hz, 2H), 7.06 (d, *J*=8.4 Hz, 2H), 4.57 (t, *J*=7.8 Hz, 1H), 3.11 (d, *J*=7.2 Hz, 2H), 2.29-2.26 (m, 5H), 1.49 (sext, *J*=7.2 Hz, 2H), 0.79 (t, *J*=7.2 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 209.0, 144.2, 140.9, 135.8, 129.1, 128.4, 127.6, 127.5, 126.2, 48.8, 45.5, 45.4, 20.9, 16.9, 7.5 ppm. IR (neat) 3085(w), 3027(m), 2962(m), 2874(w), 1714(s), 698(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{19}H_{23}O$ $[M+H]^+$ 267.1743, found 267.1744.

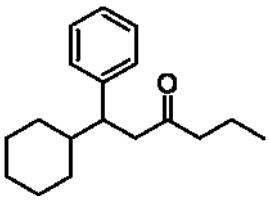


**1,3-Diphenyl-3-p-tolylpropan-1-one**[3] $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.93 (d, *J*=8.4 Hz, 2H), 7.54 (t, *J*=8.4 Hz, 2H), 7.43

(t, *J*=7.2 Hz, 4H), 7.26-7.25 (m, 4H), 7.17-7.15 (m, 3H), 7.07 (d, *J*=8.4Hz, 2H), 4.79 (t, *J*=7.2 Hz, 1H), 3.72 (d, *J*=7.2 Hz, 2H), 2.28 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 198.7, 144.4, 141.1, 137.1, 135.9, 133.0, 129.2, 128.6, 128.5, 128.0, 127.8, 127.6, 126.3, 45.5, 44.8, 21.0 ppm.

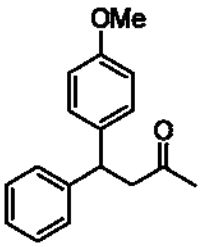


**7-Methyl-5-phenyloctan-3-one** Colorless oil. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.29-7.26 (m, 2H), 7.18-7.16 (m, 3H), 3.27-3.22 (m, 1H), 2.70-2.60 (m, 2H), 2.34-2.27 (m, 1H), 2.21-2.15 (m, 1H), 1.59-1.54 (m, 1H), 1.40-1.35 (m, 1H), 1.34-1.28 (m, 1H), 0.93 (t, *J* = 9.0 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 210.6, 144.6 128.4, 127.5, 126.2, 50.2, 45.5, 39.1, 36.7, 25.3, 23.5, 21.5, 7.5. IR (neat, $cm^{-1}$) 3062(w), 3028(w), 2954(w), 2904(m), 1714(s), 700(s). HR-MS (ESI): calcd. for $C_{15}H_{23}O$ $[M+H]^+$219.1743, found 219.1743.

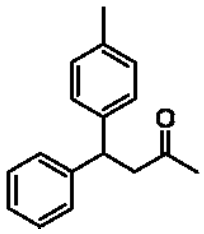


**1-Cyclohexyl-1-phenylhexan-3-one** White solid, m.p. 33-34°C.$^1$H NMR ($CDCl_3$, 600 MHz) δ 7.25 (t, *J*=7.2 Hz, 2H), 7.16 (t, *J*=7.2 Hz, 2H), 2.97-2.94 (m, 1H), 2.81-2.70 (m, 2H), 2.27-2.22 (m, 1H), 2.16-2.11 (m, 1H), 1.79-1.72 (m, 1H), 1.63-1.58 (m, 2H), 1.48-1.41 (m, 4H), 1.27-1.17 (m, 1H), 1.31-1.03 (m, 2H), 0.97-0.90 (m, 1H), 0.81-0.78 (m, 1H), 0.75 (t, *J*=7.8 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 210.5, 143.6, 128.3, 128.0, 126.1, 47.1, 46.6, 45.4, 42.9, 31.2, 30.7, 26.5, 26.3, 16.9, 13.5. IR (neat, $cm^{-1}$)3060(w), 3027(w), 2934(m), 2914(m), 2848(m), 1701(s), 740(s), 699(s). HR-MS (ESI): calcd. for $C_{18}H_{27}O$ $[M+H]^+$259.2056, found 259.2056.

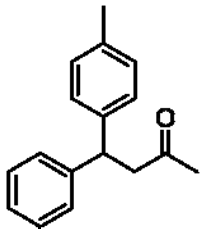
**General procedure for asymmetric sequential Aldol condensation-Rh(I)-catalyzed addition reactions of aldehydes, methyl ketones and arylboronic acids:** In a glove-box, to a vial was charged with $[RhCl(CH_2CH_2)_2]_2$ (1 mol %) and ligand (*R*)-**13** (3 equiv to Rh) and THF (0.6 mL), and the mixture was stirred at room temperature for 30 min. To another vial was charged with aldehyde (0.25 mmol), methyl ketone (0.2 mL), $K_2CO_3$ (0.25 mmol), methanol (0.1 mL) and water (0.1 mL), and the mixture was taken out of the glove-box and stirred at 50 $^oC$ for 30 min. Then the yellow mixture was brought into drybox again and mixed with arylboronic acid (0.5 mmol) and prepared catalyst solution. Finally, the mixture was stirred at 0 $^oC$ for 4-6 hours. The reaction was quenched by adding 4 N HCl (2 mL) aqueous solution. The mixture was extracted with $CH_2Cl_2$ (3 x15 mL). The organic layers were combined. After evaporation of the organic solvents, the residue was subjected to column chromatography [silica gel, ethyl acetate/hexane (v/v=1:20) as eluent] to afford the products. The product was subjected to the analysis of enantiomeric excess by HPLC with Chiralcel OD column. The absolute configuration of which was determined by comparison of its specific rotation and the retention time of the HPLC analysis with the reported one.



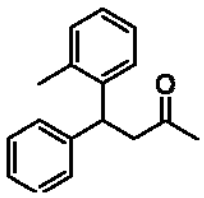

**(R)-4-(4-Methoxyphenyl)-4-phenylbutan-2-one**[5] 80 % yield. 87% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 92/8, 1.0 ml/min, 230 nm UV detector, $t_R$ = 12.05 min for (*S*) and $t_R$ = 14.08 min for (*R*)]. $^1H$ NMR ($CDCl_3$, 600 MHz) δ 7.26 (t, *J*=7.2 Hz, 4H), 7.21-7.19 (m, 2H), 7.17-7.12 (m, 3H), 6.82-6.79(m, 2H), 4.53 (t, *J*=7.2 Hz, 1H), 3.70 (s, 3H,), 3.14 (d, *J*=7.8 Hz, 1H), 2.06 (3H, s).



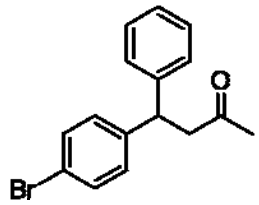
**(R)-4-Phenyl-4-*p*-tolylbutan-2-one**[6] 84 % yield. 92% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 92/8, 1.0 ml/min, 230 nm UV detector, $t_R$ = 9.06 min for (*S*) and $t_R$ = 10.57 min for (*R*)]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.27-7.24 (m, 2H), 7.21-7.20 (m, 2H), 7.17-7.14 (m, 1H), 7.11-7.06 (m, 4H), 4.57 (t, *J*=7.2 Hz, 1H), 3.13 (d, *J*=7.2 Hz, 2H), 2.28 (s, 3H), 2.06 (s, 3H).



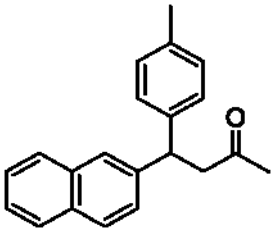
**(S)-4-Phenyl-4-*p*-tolylbutan-2-one**[6] 86 % yield. 91% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 92/8, 1.0 ml/min, 230 nm UV detector, $t_R$ = 8.68 min for (*S*) and $t_R$ = 10.44 min for (*R*)]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.27-7.24 (m, 2H), 7.21-7.20 (m, 2H), 7.17-7.14 (m, 1H), 7.11-7.06 (m, 4H), 4.57 (t, *J*=7.2 Hz, 1H), 3.13 (d, *J*=7.2 Hz, 2H), 2.28 (s, 3H), 2.06 (s, 3H).



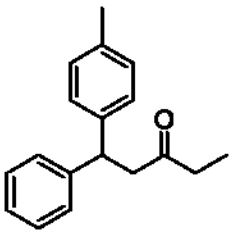
**4-Phenyl-4-*o*-tolylbutan-2-one**[2] 87 % yield. 82% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 88/12, 1.0 ml/min, 230 nm UV detector, $t_R$ = 10.08 min for (minor) and $t_R$ = 13.52 min for (major)]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.25-7.22 (m, 4H), 7.17-7.12 (m, 5H), 4.78 (t, *J*=7.2 Hz, 1H), 3.14 (d, *J*=7.2 Hz, 2H), 2.29 (s, 3H), 2.06 (s, 3H).



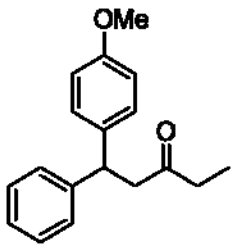
**4-(4-Bromophenyl)-4-phenylbutan-2-one** 87 % yield. 83% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 88/12, 1.0 ml/min, 230 nm UV detector, $t_R$ = 10.79 min for (major) and $t_R$ = 14.49 min for (minor)]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.38 (d, *J*=7.8 Hz, 2H), 7.27 (t, *J*=7.8 Hz, 2H), 7.18-7.17 (m, 3H), 7.09 (d, *J*=8.4 Hz, 2H), 4.55 (t, *J*=7.2 Hz, 1H), 3.15 (d, *J*=7.2 Hz, 1H), 2.07 (3H, s).



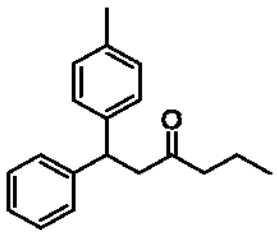
**4-(Naphthalen-2-yl)-4-p-tolylbutan-2-one** 85 % yield. 86% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 94/6, 1.0 ml/min, 230 nm UV detector, $t_R$ = 10.08 min for (minor) and $t_R$ = 13.52 min for (major)]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.77 (t, *J*=7.8 Hz, 2H), 7.73 (d, *J*=8.4 Hz, 1H), 7.67 (m, 4H), 7.45-7.40 (m, 2H), 7.31 (d, *J*=8.4 Hz, 1H), 7.15-7.03 (m, 4H), 4.71 (t, *J*=7.2 Hz, 1H), 3.25 (t, *J*=7.8 Hz, 2H), 2.28 (s, 3H), 2.09 (s, 3H).



**1-Phenyl-1-p-tolylpentan-3-one** 81 % yield. 87% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 96/4, 1.0 ml/min, 230 nm UV detector, $t_R$ = 7.67 min for (minor) and $t_R$ = 8.53 min for (major)]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.27-7.24 (m, 2H), 7.20-7.19 (m, 2H), 7.17-7.14 (m, 1H), 7.11-7.07 (m, 4H), 4.54 (t, J=7.2 Hz, 1H), 3.15 (d, J=7.2 Hz, 2H), 2.33 (q, J=7.2 Hz, 2H), 2.28 (s, 3H), 0.95 (t, J=7.2 Hz, 3H).



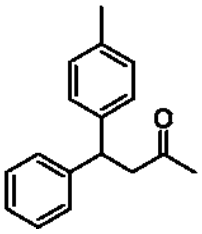

**1-(4-Methoxyphenyl)-1-phenylpentan-3-one** 80 % yield. 82% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 94/6, 1.0 ml/min, 230 nm UV detector, $t_R$ = 10.37 min for (minor) and $t_R$ = 11.39 min for (major)]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.27-7.24 (m, 2H), 7.21-7.20 (m, 2H), 7.17-7.12 (3 m, H), 6.81-6.80 (m, 2H), 4.55 (t, J=7.2 Hz, 1H), 3.75 (s, 3H), 3.11 (d, J=7.8 Hz, 2H), 2.32 (q, J=7.2 Hz, 2H), 0.95 (t, J=7.2 Hz, 3H).



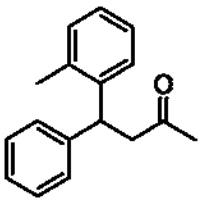

**1-Phenyl-1-p-tolylhexan-3-one** 83 % yield. 86% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 99/1, 1.0 ml/min, 230 nm UV detector, $t_R$ = 8.87 min for (minor) and $t_R$ = 9.46 min for (major)]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.24 (t, *J*=7.8 Hz, 3H), 7.21-7.19 (m, 2H), 7.14 (t, *J*=7.2 Hz, 3H), 7.10 (d, *J*=8.4 Hz, 2H), 7.06 (d, *J*=8.4 Hz, 2H), 4.57 (t, *J*=7.8 Hz, 1H), 3.11 (d, *J*=7.2 Hz, 2H), 2.29-2.26 (m, 5H), 1.49 (sext, *J*=7.2 Hz, 2H), 0.79 (t, *J*=7.2 Hz, 3H).

**General procedure for tandem aldol condensation followed by platinacycle 2-catalyzed addition reactions of aromatic aldehydes, methyl ketones and arylboronic acids:** In a dry-box, to a vial containing aldehyde (0.25 mmol), arylboronic acid (0.5 mmol), base ($K_2CO_3$, KOH or $Cs_2CO_3$ 0.75 mmol) and platinacycle **4** (0.00125 mmol) were added ketone (0.2 mL), toluene (0.8 mL) and water (7 equiv). After the mixture was stirred out of drybox at 70 $^o$C for 6-8 hours, the reaction was quenched by adding 4 N HCl (2 mL) aqueous solution. The mixture was extracted with $CH_2Cl_2$ (3 x15

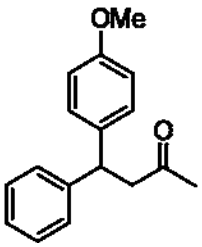
mL). The organic layers were combined. After evaporation of the organic solvents, the residue was subjected to column chromatography [silica gel, ethyl acetate/hexane (v/v=1:20) as eluent] to afford the products.



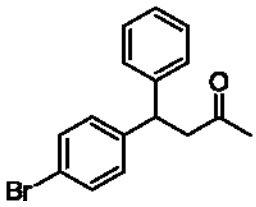
**4-Phenyl-4-*p*-tolylbutan-2-one** $^{1}$H NMR ($CDCl_3$, 600 MHz)：δ 7.27-7.24 (m, 2H), 7.21-7.20 (m, 2H), 7.17-7.14 (m, 1H), 7.11-7.06 (m, 4H), 4.57 (t, *J*=7.2 Hz, 1H), 3.13 (d, *J*=7.2 Hz, 2H), 2.28 (s, 3H), 2.06 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 206.9, 144.0, 140.7, 135.9, 129.2, 128.5, 127.6, 127.5, 126.3, 49.7, 45.6, 30.6, 20.9 ppm.



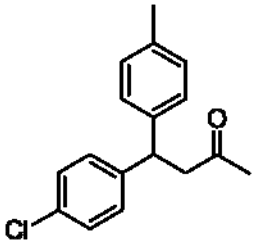
**4-Phenyl-4-*o*-tolylbutan-2-one** $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.25-7.22 (m, 4H), 7.17-7.12 (m, 5H), 4.78 (t, *J*=7.2 Hz, 1H), 3.14 (d, *J*=7.2 Hz, 2H), 2.29 (s, 3H), 2.06 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 206.8, 143.5, 141.5, 136.3, 130.8, 128.4, 127.9, 126.40, 126.2 (2C), 126.0, 50.0, 41.9, 30.6, 19.8 ppm.



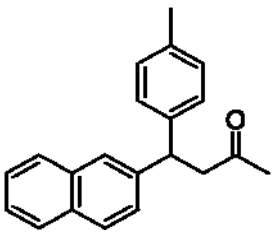

**4-(4-Methoxyphenyl)-4-phenylbutan-2-one** $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.26 (t, *J*=7.2 Hz, 4H), 7.21-7.19 (m, 2H), 7.17-7.12 (m, 3H), 6.82-6.79(m, 2H), 4.53 (t, *J*=7.2 Hz, 1H), 3.70 (s, 3H,), 3.14 (d, *J*=7.8 Hz, 1H), 2.06 (3H, s) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 207.0, 158.0, 144.2, 135.9, 128.6, 128.5, 127.5, 126.3, 113.9, 55.2, 49.8, 45.2, 30.6 ppm.



**4-(4-Bromophenyl)-4-phenylbutan-2-one** Light yellow oil. $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.38 (d, *J*=7.8 Hz, 2H), 7.27 (t, *J*=7.8 Hz, 2H), 7.18-7.17 (m, 3H), 7.09 (d, *J*=8.4 Hz, 2H), 4.55 (t, *J*=7.2 Hz, 1H), 3.15 (d, *J*=7.2 Hz, 1H), 2.07 (3H, s) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 206.3, 143.2, 142.9, 131.6, 129.4, 128.6, 127.5, 126.6, 120.2, 49.3, 45.3, 30.6 ppm. IR (neat): 3060(w), 3027(w), 2969(w), 2897(w), 1717(s), 1487(s), 699(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{16}H_{19}BrNO$ $[M+NH_4]^+$ 322.0626, found 322.0626.

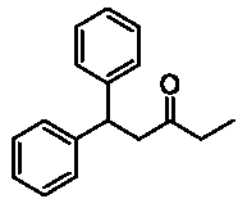


**4-(4-Chlorophenyl)-4-p-tolylbutan-2-one** White solid, m.p. 70-71°C. $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.24 (d, *J*=8.4 Hz, 2H), 7.15 (d, *J*=8.4 Hz, 2H), 7.08 (m, 4H), 4.53 (t, *J*=7.2 Hz, 1H), 3.14 (d, *J*=7.2 Hz, 2H), 2.30 (s, 3H), 2.09 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): 206.5, 142.6 140.3, 136.2, 132.1, 129.4, 129.0, 128.7, 127.4, 126.3, 49.7, 45.6, 30.6, 20.9 ppm. IR (neat) υ 3030(w), 3001(w), 2920(m), 1704(s), 1490(s), 1349(s), 762(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{17}H_{18}ClO$ $[M+H]^+$ 273.1041, found 273.1043.

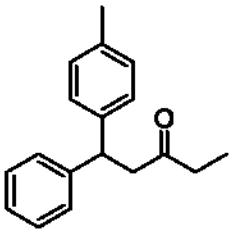


**4-(Naphthalen-2-yl)-4-p-tolylbutan-2-one** Pale yellow solid, m.p.79-80°C.$^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.77 (t, *J*=7.8 Hz, 2H), 7.73 (d, *J*=8.4 Hz, 1H), 7.67 (m, 4H), 7.45-7.40 (m, 2H), 7.31 (d, *J*=8.4 Hz, 1H), 7.15-7.03 (m, 4H), 4.71 (t, *J*=7.2 Hz, 1H), 3.25 (t, *J*=7.8 Hz, 2H), 2.28 (s, 3H), 2.09 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 206.9, 141.5, 140.7, 136.0, 133.4, 132.2, 129.3, 128.3, 127.7 (2C), 127.5, 126.5, 126.0,

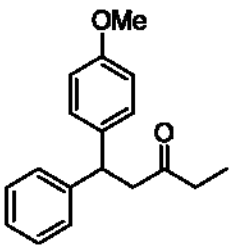
125.6, 125.5, 49.6, 45.7, 30.7, 20.9 ppm. IR (neat) 3025(w), 2968(m), 1710(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{21}H_{24}NO$ $[M+NH_4]^+$ 306.1852, found 306.1854.



**1,1-Diphenylpentan-3-one** White solid, m.p.26-27°C. $^1H$ NMR ($CDCl_3$, 600 MHz): δ 7.27-7.25 (m, 4H), 7.22-7.21 (m, 4H), 7.18-7.15 (m, 2H), 4.61 (t, J=7.2 Hz, 1H), 3.14 (d, J=7.2 Hz, 2H), 2.32 (q, J=7.2 Hz, 2H), 0.94 (t, J=7.2 Hz, 3H) ppm. $^{13}C$ NMR ($CDCl_3$, 150 MHz): δ 209. 5, 143.9, 128.5, 127.7, 126.4, 48.4, 46.0, 36.7, 7.5 ppm. IR (neat) 3028(w), 2940(w), 1710(m), 1494(m), 1452(m), 697(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{17}H_{22}NO$ $[M+NH_4]^+$ 256.1696, found 256.1697.

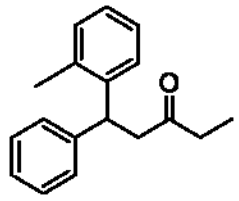


**1-Phenyl-1-p-tolylpentan-3-one** White solid, m.p. 28-29°C.$^1H$ NMR ($CDCl_3$, 600 MHz): δ 7.27-7.24 (m, 2H), 7.20-7.19 (m, 2H), 7.17-7.14 (m, 1H), 7.11-7.07 (m, 4H), 4.54 (t, J=7.2 Hz, 1H), 3.15 (d, J=7.2 Hz, 2H), 2.33 (q, J=7.2 Hz, 2H), 2.28 (s, 3H), 0.95 (t, J=7.2 Hz, 3H) ppm. $^{13}C$ NMR ($CDCl_3$, 150 MHz): δ 209.6, 144.2 141.0, 129.2, 128.5, 127.7, 127.6, 126.3, 48.6, 45.7, 36.7, 21.0, 7.6 ppm. IR (neat) 3025(w), 2921(m), 1711(s), 1514(m), 1454(m), 773(m), 726(s), 699(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{18}H_{20}NaO$ $[M+Na]^+$ 275.1406, found 275.1409.

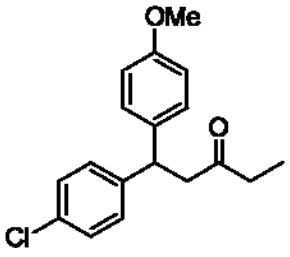



**1-(4-Methoxyphenyl)-1-phenylpentan-3-one** Light yellow oil. $^1H$ NMR ($CDCl_3$, 600 MHz): δ 7.27-7.24 (m, 2H), 7.21-7.20 (m, 2H), 7.17-7.12 (3 m, H), 6.81-6.80 (m, 2H), 4.55 (t, J=7.2 Hz,

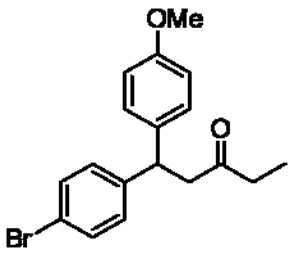
1H), 3.75 (s, 3H), 3.11 (d, J=7.8 Hz, 2H), 2.32 (q, J=7.2 Hz, 2H), 0.95 (t, J=7.2 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 209.6, 158.0 144.3, 136.1, 128.6, 128.5, 127.6, 126.3, 113.9, 55.2, 48.7, 45.3, 36.7, 7.6 ppm. IR (neat) 3060(w), 3028(w), 2973(w), 2937(w), 1714(s), 1511(s), 1248(s), 699(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{18}H_{20}NaO_2$ $[M+NH_4]^+$ 291.1356, found 291.1358.



**1-Phenyl-1-*o*-tolylpentan-3-one** Colorless oil. $^1$H NMR ($CDCl_3$, 600 MHz): δ 7.26-7.23 (m, 3H), 7.20-7.12 (m, 6H), 4.81 (t, J=7.2 Hz, 1H), 3.13 (d, J=7.2 Hz, 2H), 2.39-2.74 (m, 5H), 0.96 (t, J=7.2 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 209.6, 143.6 141.6, 136.4, 130.7, 128.4, 127.9, 126.4, 126.2, 48.8, 41.9, 36.7, 19.8, 7.5 ppm. IR (neat) 3062(w), 3025(m), 2974(m), 2938(m), 1714(s), 699(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{18}H_{24}NO$ $[M+NH_4]^+$ 270.1852, found 270.1853.

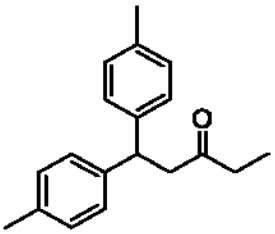


**1-(4-Chlorophenyl)-1-(4-methoxyphenyl)pentan-3-one** White solid, m.p. 50°C. $^1$H NMR ($CDCl_3$, 600 MHz): δ 7.23 (d, J=8.4 Hz, 2H), 7.14 (d, J=8.4 Hz, 2H), 7.10 (d, J=8.4 Hz, 2H), 6.82 (d, J=8.4 Hz, 2H), 4.54 (t, J=7.2 Hz, 1H), 3.76 (s, 3H), 3.10 (d, J=7.8 Hz, 2H), 2.34 (q, J=7.2 Hz, 2H), 0.96 (t, J=7.8 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 209.2, 158.2, 142.9, 135.6, 132.0, 129.0 (2C), 128.5, 114.0, 55.2, 48.4, 44.5, 36.7, 7.5 ppm. IR (neat) 2974(w), 2940(w), 2884(m), 1708(s), 1464(s), 818(s) $cm^{-1}$.Anal. Calcd for $C_{18}H_{19}ClO_2$: C, 71.40; H, 6.32; Found: C, 71.47; H, 6.32.



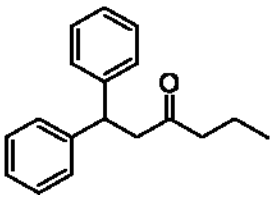

**1-(4-Bromophenyl)-1-(4-methoxyphenyl)pentan-3-one**

Colorless oil. $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.38 (d, *J*=9.0 Hz, 2H), 7.10 (d, *J*=8.4 Hz, 2H), 7.08 (d, *J*=8.4 Hz, 2H), 6.82-6.81 (m, 2H), 4.52 (t, J=7.2 Hz, 1H), 3.76 (s, 3H), 3.09 (d, *J*=7.8 Hz, 2H), 2.34 (q, *J*=7.2 Hz, 2H), 0.96 (t, *J*=7.2 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 209.2, 158.2, 143.4, 135.5, 131.5, 129.3, 128.5, 120.1, 114.0, 55.2, 48.4, 44.6, 36.7, 7.5 ppm. IR (neat) υ 2972(w), 2936(w), 2903(w), 2835(w), 1714(s), 1511(s), 1248(s) $cm^{-1}$. Anal. Calcd for $C_{18}H_{19}BrO_2$: C, 62.26; H, 5.52; Found: C, 62.10; H, 5.46.



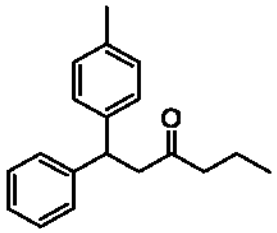

**1,1-Di*p*-tolylpentan-3-one**

White solid, m.p. 83-84$^{o}$C. $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.10-7.05 (m, 8H), 4.53 (t, *J*=7.8 Hz, 1H), 3.76 (s, 3H), 3.11 (d, *J*=7.2 Hz, 2H), 2.32 (q, *J*=7.2 Hz, 2H), 2.78 (s, 6H), 0.96 (t, *J*=7.2 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 209.7, 141.2, 135.8, 129.2, 127.5, 48.6, 45.3, 36.7, 20.9, 7.5 ppm. IR (neat) 2980(m), 2923(m), 1712(s), 1512(m), 1373(m), 1108(s), 805(s) $cm^{-1}$. Anal. Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.32; Found: C, 85.51; H, 8.34.

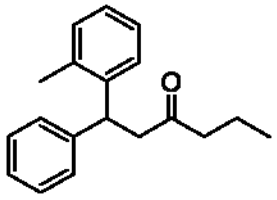



**1,1-Diphenylhexan-3-one** Light yellow oil. $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.27-7.14 (m, 10H), 4.61 (t, *J*=7.8 Hz, 1H), 3.13 (d, *J*=7.2 Hz, 2H), 2.30-2.27 (m, 2H), 1.53-1.46 (m, 2H), 0.79 (t, *J*=7.2 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 208.9,

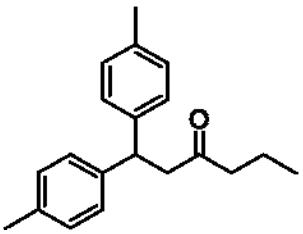
143.9, 128.5, 127.7, 126.3, 48.7, 45.9, 45.4, 16.9, 13.5 ppm. IR (neat) 3061(w), 3028(w), 2961(w), 2874(w), 1712(m), 698(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{18}H_{20}NaO$ $[M+Na]^+$ 275.1406, found 275.1408.



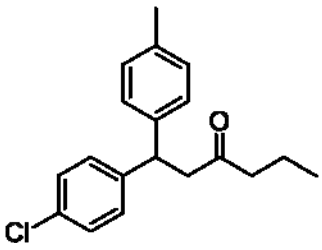
**1-Phenyl-1-p-tolylhexan-3-one** Light yellow oil. $^1H$ NMR ($CDCl_3$, 600 MHz): δ 7.24 (t, *J*=7.8 Hz, 3H), 7.21-7.19 (m, 2H), 7.14 (t, *J*=7.2 Hz, 3H), 7.10 (d, *J*=8.4 Hz, 2H), 7.06 (d, *J*=8.4 Hz, 2H), 4.57 (t, *J*=7.8 Hz, 1H), 3.11 (d, *J*=7.2 Hz, 2H), 2.29-2.26 (m, 5H), 1.49 (sext, *J*=7.2 Hz, 2H), 0.79 (t, *J*=7.2 Hz, 3H) ppm. $^{13}C$ NMR ($CDCl_3$, 150 MHz): δ 209.0, 144.2, 140.9, 135.8, 129.1, 128.4, 127.6, 127.5, 126.2, 48.8, 45.5, 45.4, 20.9, 16.9, 7.5 ppm. IR (neat) 3085(w), 3027(m), 2962(m), 2874(w), 1714(s), 698(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{19}H_{23}O$ $[M+H]^+$ 267.1743, found 267.1744.



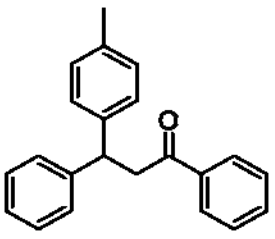
**1-Phenyl-1-*o*-tolylhexan-3-one** Light yellow oil. $^1H$ NMR ($CDCl_3$, 600 MHz): δ 7.25-7.22 (m, 3H), 7.18-7.12 (m, 6H), 4.80 (t, *J*=7.2 Hz, 1H), 3.11 (d, *J*=7.2 Hz, 2H), 2.34-2.23 (m, 5H), 1.50 (sext, *J*=7.2 Hz, 2H), 0.80 (t, *J*=7.2 Hz, 3H) ppm. $^{13}C$ NMR ($CDCl_3$, 150 MHz): δ 209.1, 143.6, 141.6, 136.4, 130.7, 128.4, 127.9, 126.4, 126.0, 49.1, 45.5, 41.8, 19.8, 16.9, 13.6 ppm. IR (neat) 3062(w), 3025(m), 2974(m), 2938(m), 1714(s), 699(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{19}H_{23}O$ $[M+H]^+$ 267.1743, found 267.1743.



**1,1-Di*p*-tolylhexan-3-one** White solid, m.p. 53-54°C. $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.10-7.05 (m, 8H), 4.52 (t, *J*=7.8 Hz, 1H), 3.10 (d, *J*=7.8 Hz, 2H), 2.30-2.27 (m, 8H), 1.50 (sext, *J*=7.2 Hz, 2H), 0.80 (t, *J*=7.2 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 209.2, 141.2, 135.7, 129.2, 127.5, 48.9, 45.4, 45.2, 20.9, 16.9, 13.6 ppm. IR (neat) 2963(m), 2921(m), 2882(m), 1713(s), 1512(m), 1319(m), 769(s) $cm^{-1}$. Anal. Calcd for $C_{20}H_{24}O$: C, 85.67; H, 8.63; Found: C, 85.63; H, 8.73.



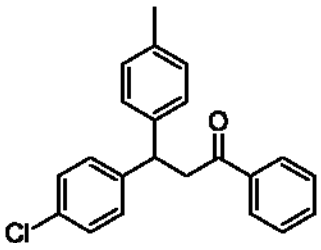
**1-(4-Chlorophenyl)-1-p-tolylhexan-3-one**White solid, m.p. 49-50°C. $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.22-7.20 (m, 2H), 7.13 (d, J=8.4 Hz, 2H), 7.07 ( s, 4H), 4.54 (t, *J*=7.8 Hz, 1H), 3.09 (d, *J*=7.2 Hz, 2H), 2.30-2.28 (m, 5H), 1.51 (sext, *J*=7.2 Hz, 2H), 0.81 (t, *J*=7.8 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 208.7, 142.8, 140.4, 136.1, 132.0, 129.3, 129.0, 128.5, 127.4, 48.6, 45.4, 44.8, 20.9, 16.9, 13.5 ppm. IR (neat) 3052(w), 2957(m), 2925(s), 2854(m), 1709(s), 1488(s), 807(s) $cm^{-1}$. HR-MS (ESI): calcd. for $C_{15}H_{29}ClNO$ $[M+NH_4]^+$ 318.1619, found 318.1619.



**1,3-Diphenyl-3-p-tolylpropan-1-one** $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.93 (d, *J*=8.4 Hz, 2H), 7.54 (t, *J*=8.4 Hz, 2H), 7.43 (t, *J*=7.2 Hz, 4H), 7.26-7.25 (m, 4H), 7.17-7.15 (m, 3H), 7.07 (d, *J*=8.4Hz, 2H), 4.79 (t, *J*=7.2 Hz, 1H), 3.72 (d, *J*=7.2 Hz, 2H), 2.28 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 198.7, 144.4, 141.1, 137.1, 135.9,

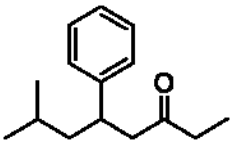
133.0, 129.2, 128.6, 128.5, 128.0, 127.8, 127.6, 126.3, 45.5, 44.8, 21.0 ppm.

**3-(4-Chlorophenyl)-1-phenyl-3-p-tolylpropan-1-one**

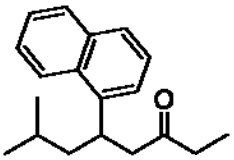


White solid, m.p. 93-94$^{o}$C. $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.92 (d, *J*=8.4 Hz, 2H), 7.54 (t, *J*=7.2 Hz, 1H), 7.43 (t, *J*=7.2 Hz, 2H), 7.23-7.11 (m, 4H), 7.13-7.07 (m, 4H), 4.76 (t, *J*=7.8 Hz, 1H), 3.72 (d, *J*=7.2 Hz, 2H), 2.28 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz) δ 197.7, 142.8, 140.7, 136.9, 136.1, 133.1, 132.0, 129.3, 129.1, 128.6, 128.0, 127.5, 45.5, 44.9, 44.5, 20.9 ppm. IR (neat) 3024(w), 2970(w), 2923(w), 2853(w), 1672(m), 1447(m), 689(s) cm$^{-1}$. HR-MS (ESI): calcd. for $C_{22}H_{20}KO$ $[M+K]^+$ 339.1146, found 339.1148.

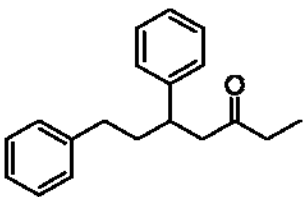
**General procedure for platinacycle 4-catalyzed tandem reactions of aliphatic aldehydes, methyl ketones and arylboronic acids**: To a vial containing aldehyde (0.25 mmol), arylboronic acid (0.5 mmol, 2 equiv), KOH ( 0.75 mmol, 3 equiv.) and platinacycle **4** (0.00125 mmol) was added ketone (0.2 mL) toluene (0.8 mL) and water (0.1 mL). After the mixture was stirred at 70 $^{o}$C for 6 hours, the reaction was quenched by adding 4 N HCl (2 mL) aqueous solution. The mixture was extracted with $CH_2Cl_2$ (3 x 15 mL). The organic layers were combined. After evaporation of the organic solvents, the residue was subjected to column chromatography [silica gel, ethyl acetate/hexane (v/v=1:20) as eluent] to afford the products.



**7-Methyl-5-phenyloctan-3-one**: colorless oil. $^{1}$H NMR δ 7.29-7.26 (m, 2H), 7.18-7.16 (m, 3H), 3.27-3.22 (m, 1H), 2.70-2.60 (m, 2H), 2.34-2.27 (m, 1H), 2.21-2.15 (m, 1H), 1.59-1.54 (m, 1H), 1.40-1.35 (m, 1H), 1.34-1.28 (m, 1H), 0.93 (t, *J* = 9.0 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H). $^{13}$C NMR δ 210.6, 144.6 128.4, 127.5, 126.2, 50.2, 45.5, 39.1, 36.7, 25.3, 23.5, 21.5, 7.5. IR 3062(w), 3028(w), 2954(w), 2904(m), 1714(s), 700(s). HR-MS (ESI+): calcd. for $C_{15}H_{23}O$ $[M+H]^{+}$219.1743, found 219.1743.

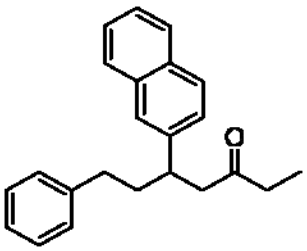


**7-Methyl-5-(naphthalen-1-yl)octan-3-one**: light yellow oil. $^{1}$H NMR δ 8.22 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 6.6 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 4.24 (br, 1H), 2.76 (br, 2H), 2.34-2.22 (m, 2H), 1.78 (br, 1H), 1.57-1.52 (m, 1H), 1.44-1.41 (m, 1H), 0.93 (t, *J* = 7.2 Hz, 3H), 0.91-0.87 (m, 6H). $^{13}$C NMR δ 210.5, 141.2, 134.0, 131.7, 128.9, 126.6, 126.0, 125.4, 123.0, 50.3, 45.2, 36.6, 31.9, 25.6, 23.3, 22.2, 7.6. IR 3046(w), 2956(m), 2904(m), 2869(m), 1713(s), 777(s). HR-MS (ESI+): calcd. for $C_{19}H_{28}NO$ $[M+NH_4]^{+}$286.2165, found 286.2167.

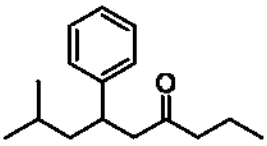


**5,7-Diphenylheptan-3-one**: light yellow oil. $^{1}$H NMR δ 7.31 (d, *J* = 7.8 Hz, 1H), 7.25-7.19 (m, 5H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.09 (d, *J* = 7.2 Hz, 2H), 3.21-3.16 (m, 1H), 2.74-2.67 (m, 2H), 2.46-2.41 (m, 2H), 2.32-2.26 (m, 1H), 2.22-2.15 (m, 1H), 2.00-1.94 (m, 1H), 1.91-1.85 (m, 1H), 0.93 (t, *J* = 7.2 Hz, 3H). $^{13}$C

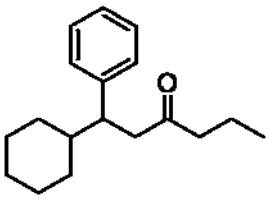
NMR δ 210.3, 144.1, 142.0, 128.5 128.3 (2C), 127.5, 126.4, 125.7, 49.8, 41.0, 38.0, 36.6, 33.6, 7.5. IR 3061(w), 3027(w), 2975(w), 2938(w), 1713(s), 699(s). HR-MS (ESI): calcd. for $C_{19}H_{23}O$ $[M+H]^+$267.1743, found 267.1745.



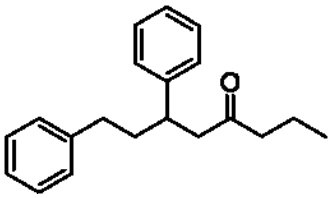
**5-(Naphthalen-2-yl)-7-phenylheptan-3-one**: light yellow oil. $^1$H NMR δ 7.81 (d, *J* = 9.0 Hz, 3H), 7.64 (s, 1H), 7.48-7.43 (m, 2H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 2H),), 7.15 (t, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 7.2 Hz, 2H), 3.40-3.35 (m, 1H), 2.85-2.75 (m, 2H), 2.51-2.42 (m, 2H), 2.35-2.28 (m, 1H), 2.23-2.16 (m, 1H), 2.08-1.96 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR δ 210.2, 142.0, 141.5, 133.5 132.4, 128.3(3C), 127.6(2C), 126.3, 126.0, 125.7, 125.6, 125.4, 49.7, 41.0, 37.9, 36.7, 33.7, 7.5. IR 3058(w), 3025(w), 2973(w), 2937(m), 1712(s), 746(s). HR-MS (ESI+): calcd. for $C_{23}H_{28}NO$ $[M+NH_4]^+$334.2165, found 334.2161.



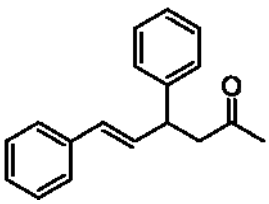
**8-Methyl-6-phenylnonan-4-one**: light yellow oil. $^1$H NMR δ 7.28-7.26 (m, 2H), 7.18-7.16 (m, 2H), 3.27-3.22 (m, 1H), 2.69-2.58 (m, 2H), 2.30-2.22 (m, 1H), 2.18-2.13 (m, 1H), 1.58-1.54 (m, 1H), 1.51-1.44 (m, 2H), 1.39-1.34 (m, 1H), 1.32-1.28 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.81-0.78 (m, 6H). $^{13}$C NMR δ 210.1, 144.6 128.4, 127.5, 126.2, 50.5, 45.5 (2C), 39.0, 25.3, 23.5, 21.5, 16.9, 13.6. IR 3085(w), 3063(w), 3028(w), 2957(m), 1714(s), 700(s). HR-MS (ESI+): calcd. for $C_{16}H_{28}NO$ $[M+NH_4]^+$ 250.2165, found 250.2166.



**1-Cyclohexyl-1-phenylhexan-3-one**: white solid, mp 33-34$^{o}$C. $^{1}$H NMR δ 7.25 (t, *J* = 7.2 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 2H), 2.97-2.94 (m, 1H), 2.81-2.70 (m, 2H), 2.27-2.22 (m, 1H), 2.16-2.11 (m, 1H), 1.79-1.72 (m, 1H), 1.63-1.58 (m, 2H), 1.48-1.41 (m, 4H), 1.27-1.17 (m, 1H), 1.31-1.03 (m, 2H), 0.97-0.90 (m, 1H), 0.81-0.78 (m, 1H), 0.75 (t, *J*=7.8 Hz, 3H). $^{13}$C NMR δ 210.5, 143.6, 128.3, 128.0, 126.1, 47.1, 46.6, 45.4, 42.9, 31.2, 30.7, 26.5, 26.3, 16.9, 13.5. IR 3060(w), 3027(w), 2934(m), 2914(m), 2848(m), 1701(s), 740(s), 699(s). HR-MS (ESI+): calcd. for $C_{18}H_{27}O$ $[M+H]^{+}$259.2056, found 259.2056.



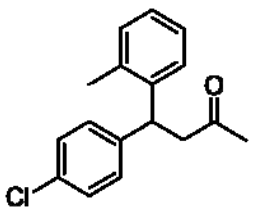
**6,8-Diphenyloctan-4-one**: light yellow oil. $^{1}$H NMR δ 7.31 (d, *J* = 7.8 Hz, 1H), 7.25-7.20 (m, 5H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.09 (d, *J* = 7.2 Hz, 2H), 3.21-3.16 (m, 1H), 2.74-2.66 (m, 2H), 2.45-2.41 (m, 2H), 2.27-2.22 (m, 1H), 2.19-2.14 (m, 1H), 1.99-1.94 (m, 1H), 1.91-1.85 (m, 1H), 1.51-1.45 (m, 1H), 0.79 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR δ 209.9, 144.1, 142.0, 128.5, 128.3 (2C), 127.6, 126.4, 125.7, 50.1, 45.4, 40.9, 38.0, 33.6, 17.0, 13.6. IR 3062(w), 3027(w), 2961(m), 2874(w), 1713(m), 1494(m), 1453(m), 699(s). HR-MS (ESI+): calcd. for $C_{20}H_{28}NO$ $[M+NH_4]^{+}$ 298.2165, found 298.2167.



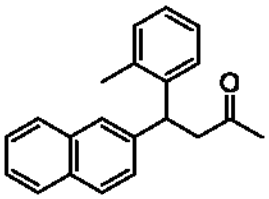
**4,6-Diphenylhex-5-en-2-one**: $^{1}$H NMR δ 7.34-7.17 (m, 10H), 6.39-6.30 (m, 2H), 4.08 (q, *J* = 7.2 Hz, 1H), 7.09 (d, *J* = 7.2 Hz, 2H), 2.98-2.90 (m, 2H), 2.11 (s, 3H). $^{13}$C NMR δ 206.9,

142.9, 137.0, 132.3, 129.9, 128.7, 128.4, 127.6, 127.3, 126.7, 126.2, 49.4, 43.9, 30.7.

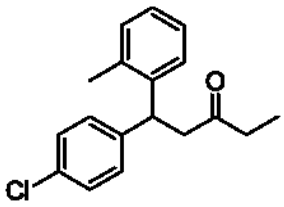
**General procedure for tandem aldol condensation-$[Rh(COD)Cl]_2$-catalyzed addition reactions of aldehydes, methyl ketones and arylboronic acids:** In a glove-box, to a vial containing aldehyde (0.25 mmol) and KOH (0.75 mmol) were added ketone (0.2 mL), methanol (0.1 mL) and water (0.1 mL). After the mixture was stirred at 50 - 60 $^{o}$C for 30 min, arylboronic acid (0.5 mmol), THF (1 mL) and $[Rh(COD)Cl]_2$ or palladacycle **3** (0.0025 mmol) (an Ohaus Explorer analytic balance with 0.1 mg accuracy was used for weighing the catalysts) were added into reaction mixture and then stirred at room temperature for another 6 hours. The reaction was quenched by adding 4 N HCl (2 mL) aqueous solution. The mixture was extracted with $CH_2Cl_2$ (3 x15 mL). The organic layers were combined. After evaporation of the organic solvents, the residue was subjected to column chromatography [silica gel, ethyl acetate/hexane (v/v=1:20) as eluent] to afford the products.



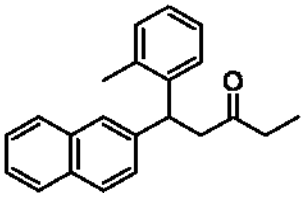

**4-(4-Chlorophenyl)-4-*o*-tolylbutan-2-one** Light yellow liquid. $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.24 (d, *J*=8.4 Hz, 2H), 7.15 (d, *J*=8.4 Hz, 2H), 7.08 (m, 4H), 4.53 (t, *J*=7.2 Hz, 1H), 3.14 (d, *J*=7.2 Hz, 2H), 2.30 (s, 3H), 2.09 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): 206.5, 142.6 140.3, 136.2, 132.1, 129.4, 129.0, 128.7, 127.4, 126.3, 49.7, 45.6, 30.6, 20.9 ppm. IR (neat) υ 3030(w), 3001(w), 2920(m), 1704(s), 1490(s), 1349(s), 762(s) cm$^{-1}$. HR-MS (ESI): calcd. for $C_{17}H_{18}ClO$ $[M+H]^+$ 273.1041, found 273.1043.



**4-(Naphthalen-2-yl)-4-*o*-tolylbutan-2-one** Pale yellow solid, m.p.79-80$^{o}$C.$^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.75 (t, *J*=8.4 Hz, 2H), 7.71 (d, *J*=9.0 Hz, 1H), 7.60 (s, 1H), 7.44-7.39 (m, 2H), 7.30 (d, *J*=8.4 Hz, 1H), 7.27 (d, *J*=7.8 Hz, 1H), 7.22-7.18 (m, 1H), 7.14-7.13 (m, 2H), 4.95 (t, *J*=7.2 Hz, 1H), 3.25 (t, *J*=7.2 Hz, 2H), 2.33 (s, 3H), 2.08 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 206.8, 141.4, 140.9, 136.4, 133.4, 132.1, 130.8, 128.2, 127.7, 127.5, 126.6, 126.5, 126.4, 126.1 (2C), 126.0, 125.5, 49.8, 42.0, 30.7, 19.9 ppm. IR (neat) 3025(w), 2968(m), 1710(s) cm$^{-1}$. HR-MS (ESI): calcd. for $C_{21}H_{24}NO$ $[M+NH_4]^+$ 306.1852, found 306.1854.

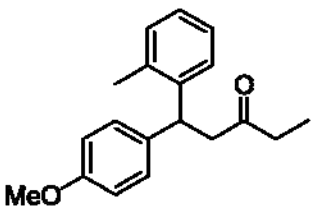


**1-(4-Chlorophenyl)-1-*o*-tolylpentan-3-one** Colorless liquid. $^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.21-7.17 (m, 4H), 7.12-7.07 (m, 4H), 4.78 (t, J=9.0 Hz, 1H), 3.09 (d, J=8.4 Hz, 2H), 2.42-2.24 (m, 2H), 2.27 (s, 3H), 0.96 (t, J=7.8 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 209.1, 142.2, 141.2, 136.3, 131.9, 130.9, 129.3, 128.5, 126.6, 126.1, 48.6, 41.2, 36.7, 19.7, 7.5 ppm. IR (neat) 2974(w), 2940(w), 2884(m), 1708(s), 1464(s), 818(s) cm$^{-1}$.Anal. Calcd for $C_{18}H_{19}ClO_2$: C, 71.40; H, 6.32; Found: C, 71.47; H, 6.32.

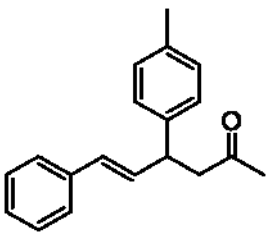


**1-(Naphthalen-2-yl)-1-o-tolylpentan-3-one** Pale yellow solid, m.p.79-80$^{o}$C.$^{1}$H NMR ($CDCl_3$, 600 MHz): δ 7.75 (t, *J*=8.4 Hz, 2H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.59 (s, 1H), 7.44-7.39 (m, 2H), 7.30 (d, *J* = 9.0 Hz, 1H), 7.28 (d, *J* = 7.8

Hz, 1H), 7.21-7.18 (m, 1H), 7.13-7.12 (m, 2H), 4.97 (t, *J* = 8.4 Hz, 1H), 3.21 (t, *J* = 7.8 Hz, 2H), 2.41-2.28 (m, 2H), 2.33 (s, 3H), 0.95 (t, *J* = 7.2 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 209.5, 141.5, 141.1, 136.5, 133.4, 132.1, 130.8, 128.1, 127.7, 127.5, 126.7, 126.5, 126.4, 126.1 (2C), 126.0, 125.5, 48.7, 42.0, 36.8, 19.9 7.5 ppm. IR (neat) 3025(w), 2968(m), 1710(s) $cm^{-1}$.



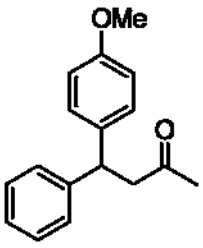

**1-(4-Methoxyphenyl)-1-*o*-tolylpentan-3-one** Colorless oil. $^1$H NMR ($CDCl_3$, 600 MHz): δ 7.25-7.05 (m, 6H), 7.10 (d, *J*=8.4 Hz, 2H), 6.80-6.76 (m, 2H), 4.74 (t, J = 7.2 Hz, 1H), 3.74 (s, 3H), 3.09 (d, *J* = 8.4 Hz, 2H), 2.43-2.20 (m, 2H), 2.29 (s, 3H), 0.95 (t, *J*=7.2 Hz, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 150 MHz): δ 209.8, 157.9, 141.9, 136.2, 135.7, 130.7, 128.9, 126.3, 126.0 (2C), 113.8, 55.1, 48.9, 41.1, 36.8, 19.8, 7.5 ppm.



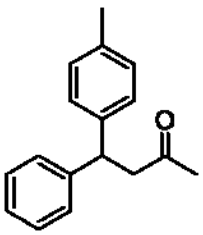

**6-Phenyl-4-*p*-tolylhex-5-en-2-one**: $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.33-7.11 (m, 9H), 6.40-6.26 (m, 2H), 4.04 (q, *J* = 7.5 Hz, 1H), 2.94-2.90 (m, 2H), 2.31 (s, 3H), 2.10 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 207.0, 139.8, 137.1, 136.2, 132.5, 129.7, 129.3, 128.4, 127.5, 127.2, 126.2, 49.4, 43.9, 30.7.

**General procedure for asymmetric tandem Aldol condensation-Rh(I)-catalyzed addition reactions of aldehydes, methyl ketones and arylboronic acids:** In a glove-box, to a vial was charged with $[RhCl(CH_2CH_2)_2]_2$ (1 mol %) and ligand

(3*R*,6*R*)-**10b** (1.2 equiv to Rh) and THF (0.2 mL), and the mixture was stirred at room temperature for 30 min. To another vial was charged with aldehyde (0.25 mmol), methyl ketone (0.2 mL), arylboronic acids (0.375 mmol), $K_2CO_3$ (0.25 mmol), methanol (0.5 mL) and water (0.1 mL), prepared catalyst solution was dropwise added. The mixture was then taken out of the glove-box and stirred at room temperature for 20-24 hours. The reaction was quenched by adding 4 N HCl (2 mL) aqueous solution. The mixture was extracted with $CH_2Cl_2$ (3 x15 mL). The organic layers were combined. After evaporation of the organic solvents, the residue was subjected to column chromatography [silica gel, ethyl acetate/hexane (v/v=1:20) as eluent] to afford the products. The product was subjected to the analysis of enantiomeric excess by HPLC with Chiralcel OD column. The absolute configuration of which was determined by comparison of its specific rotation and the retention time of the HPLC analysis with the reported one.

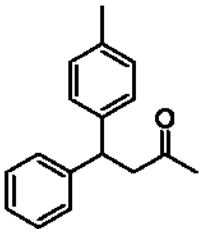



**(R)-4-(4-Methoxyphenyl)-4-phenylbutan-2-one** 81 % yield. 93% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 92/8, 1.0 ml/min, 230 nm UV detector, $t_R$ = 11.98 min for (*S*) and $t_R$ = 14.17 min for (*R*)]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.26 (t, *J*=7.2 Hz, 4H), 7.21-7.19 (m, 2H), 7.17-7.12 (m, 3H), 6.82-6.79(m, 2H), 4.53 (t, *J*=7.2 Hz, 1H), 3.70 (s, 3H,), 3.14 (d, *J*=7.8 Hz, 1H), 2.06 (3H, s).

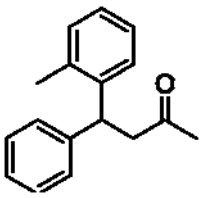



**(R)-4-Phenyl-4-*p*-tolylbutan-2-one** 84 % yield. 83% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 92/8, 1.0 ml/min, 230 nm UV detector, $t_R$ = 9.32 min for (*S*) and $t_R$ = 11.29

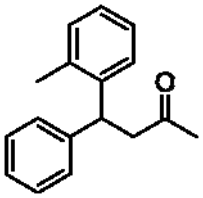
min for (*R*)]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.27-7.24 (m, 2H), 7.21-7.20 (m, 2H), 7.17-7.14 (m, 1H), 7.11-7.06 (m, 4H), 4.57 (t, *J*=7.2 Hz, 1H), 3.13 (d, *J*=7.2 Hz, 2H), 2.28 (s, 3H), 2.06 (s, 3H).



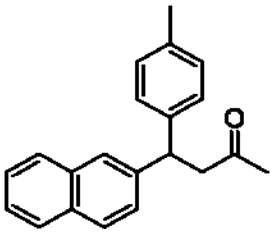
**(S)-4-Phenyl-4-*p*-tolylbutan-2-one** 90 % yield. 92% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 92/8, 1.0 ml/min, 230 nm UV detector, $t_R$ = 8.68 min for (*S*) and $t_R$ = 10.44 min for (*R*)]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.27-7.24 (m, 2H), 7.21-7.20 (m, 2H), 7.17-7.14 (m, 1H), 7.11-7.06 (m, 4H), 4.57 (t, *J*=7.2 Hz, 1H), 3.13 (d, *J*=7.2 Hz, 2H), 2.28 (s, 3H), 2.06 (s, 3H).



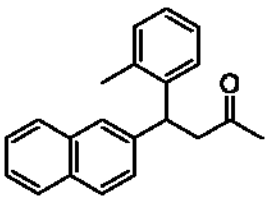
**4-Phenyl-4-*o*-tolylbutan-2-one** 89 % yield. 98% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 88/12, 1.0 ml/min, 230 nm UV detector, $t_R$ = 10.20 min for (minor) and $t_R$ = 13.85 min for (major)]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.25-7.22 (m, 4H), 7.17-7.12 (m, 5H), 4.78 (t, *J*=7.2 Hz, 1H), 3.14 (d, *J*=7.2 Hz, 2H), 2.29 (s, 3H), 2.06 (s, 3H).



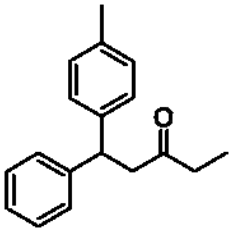
**4-Phenyl-4-*o*-tolylbutan-2-one** 83 % yield. 84% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 88/12, 1.0 ml/min, 230 nm UV detector, $t_R$ = 10.02 min for (major) and $t_R$ = 14.25 min for (minor)]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.25-7.22 (m, 4H), 7.17-7.12 (m, 5H), 4.78 (t, *J*=7.2 Hz, 1H), 3.14 (d, *J*=7.2 Hz, 2H), 2.29 (s, 3H), 2.06 (s, 3H).



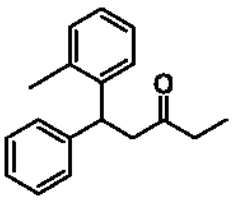
**4-(Naphthalen-2-yl)-4-p-tolylbutan-2-one** 84 % yield. 92% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 94/6, 1.0 ml/min, 230 nm UV detector, $t_R$ = 12.58 min for (minor) and $t_R$ = 15.60 min for (major)]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.77 (t, *J*=7.8 Hz, 2H), 7.73 (d, *J*=8.4 Hz, 1H), 7.67 (m, 4H), 7.45-7.40 (m, 2H), 7.31 (d, *J*=8.4 Hz, 1H), 7.15-7.03 (m, 4H), 4.71 (t, *J*=7.2 Hz, 1H), 3.25 (t, *J*=7.8 Hz, 2H), 2.28 (s, 3H), 2.09 (s, 3H).



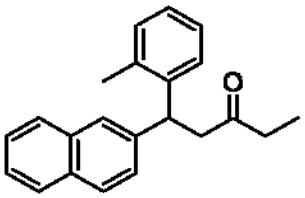
**4-(Naphthalen-2-yl)-4-*o*-tolylbutan-2-one** 86 % yield. 96% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 90/10, 1.0 ml/min, 230 nm UV detector, $t_R$ = 13.19 min for (minor) and $t_R$ = 14.94 min for (major)]. $^1$H NMR ($CDCl_3$, 600 MHz): δ 7.75 (t, *J*=8.4 Hz, 2H), 7.71 (d, *J*=9.0 Hz, 1H), 7.60 (s, 1H), 7.44-7.39 (m, 2H), 7.30 (d, *J*=8.4 Hz, 1H), 7.27 (d, *J*=7.8 Hz, 1H), 7.22-7.18 (m, 1H), 7.14-7.13 (m, 2H), 4.95 (t, *J*=7.2 Hz, 1H), 3.25 (t, *J*=7.2 Hz, 2H), 2.33 (s, 3H), 2.08 (s, 3H) ppm.



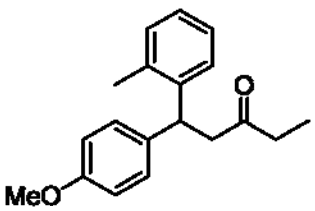
**1-Phenyl-1-p-tolylpentan-3-one** 87 % yield. 93% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 96/4, 1.0 ml/min, 230 nm UV detector, $t_R$ = 7.74 min for (minor) and $t_R$ = 8.72min for (major)]. $^1$H NMR ($CDCl_3$, 600 MHz) δ 7.27-7.24 (m, 2H), 7.20-7.19 (m, 2H), 7.17-7.14 (m, 1H), 7.11-7.07 (m, 4H), 4.54 (t, J=7.2 Hz, 1H), 3.15 (d, J=7.2 Hz, 2H), 2.33 (q, J=7.2 Hz, 2H), 2.28 (s, 3H), 0.95 (t, J=7.2 Hz, 3H).



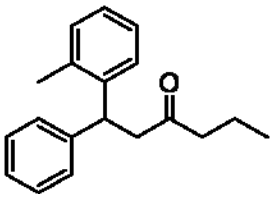
**1-Phenyl-1-*o*-tolylpentan-3-one** 86 % yield. 99% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 98/2, 1.0 ml/min, 230 nm UV detector, $t_R$ = 10.74 min for (minor) and $t_R$ = 14.83 min for (major)]. $^1$H NMR ($CDCl_3$, 600 MHz): δ 7.26-7.23 (m, 3H), 7.20-7.12 (m, 6H), 4.81 (t, J=7.2 Hz, 1H), 3.13 (d, J=7.2 Hz, 2H), 2.39-2.74 (m, 5H), 0.96 (t, J=7.2 Hz, 3H) ppm.



**1-(Naphthalen-2-yl)-1-o-tolylpentan-3-one** 84 % yield. 98% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 98/2, 1.0 ml/min, 230 nm UV detector, $t_R$ = 14.67 min for (minor) and $t_R$ = 17.85 min for (major)]. $^1$H NMR ($CDCl_3$, 600 MHz): δ 7.75 (t, *J*=8.4 Hz, 2H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.59 (s, 1H), 7.44-7.39 (m, 2H), 7.30 (d, *J* = 9.0 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.21-7.18 (m, 1H), 7.13-7.12 (m, 2H), 4.97 (t, *J* = 8.4 Hz, 1H), 3.21 (t, *J* = 7.8 Hz, 2H), 2.41-2.28 (m, 2H), 2.33 (s, 3H), 0.95 (t, *J* = 7.2 Hz, 3H) ppm.



**1-(4-Methoxyphenyl)-1-*o*-tolylpentan-3-one** 81 % yield. 99% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 99/1, 0.5 ml/min, 230 nm UV detector, $t_R$ = 33.27 min for (major) and $t_R$ = 36.15 min for (minor)].. $^1$H NMR ($CDCl_3$, 600 MHz): δ 7.25-7.05 (m, 6H), 7.10 (d, *J*=8.4 Hz, 2H), 6.80-6.76 (m, 2H), 4.74 (t, J = 7.2 Hz, 1H), 3.74 (s, 3H), 3.09 (d, *J* = 8.4 Hz, 2H), 2.43-2.20 (m, 2H), 2.29 (s, 3H), 0.95 (t, *J*=7.2 Hz, 3H) ppm.



**1-Phenyl-1-*o*-tolylhexan-3-one** 82 % yield. 96% ee. [HPLC condition: Chiralcel OD column, *n*-hexane/2-propanol = 99/1, 1.0 ml/min, 230 nm UV detector, $t_R$ = 10.58 min for (minor) and $t_R$ = 14.18 min for (major)]. $^1$H NMR ($CDCl_3$, 600 MHz): δ 7.25-7.22 (m, 3H), 7.18-7.12 (m, 6H), 4.80 (t, *J*=7.2 Hz, 1H), 3.11 (d, *J*=7.2 Hz, 2H), 2.34-2.23 (m, 5H), 1.50 (sext, *J*=7.2 Hz, 2H), 0.80 (t, *J*=7.2 Hz, 3H) ppm.

## Bibliography


1 (a) Luderer, M. R.; Bailey, W. F.; Luderer, M. R.; Fair, J. D.; Dancer, R. J.;Sommer, M. B. *Tetrahedron: Asymmetry* **2009**, *20,* 981-998; (b) Alexakis, A.; Vuagnoux-d'Augustin, M.; Martin, D.;Kehrli, S. *Latv. Kim. Z.* **2007**, 373-377; (c) Wang, D.;Chan, T. H. *Sci. Synth.* **2002**, *4,* 481-498; (d) Hua, D. H.; Chen, Y.;Millward, G. S. *Sulfur Rep.* **1999**, *21,* 211-239

2 (a) Allendorf, M. D.;van, M. A. M. B. *Top. Organomet. Chem.* **2005**, *9,* 1-48; (b) ; (c) ; (d) ; (e) Weickgenannt, A.;Oestreich, M. *Chem.--Eur. J.* **2010**, *16,* 402-412

3 (a) Binder, C. M.;Singaram, B. *Org. Prep. Proced. Int.* **2011**, *43,* 139-208; (b) Blackmond, D. *Chem. Br.* **2002**, *38,* 34-37; (c) Braese, S.; Dahmen, S.; Hoefener, S.; Lauterwasser, F.; Kreis, M.;Ziegert, R. E. *Synlett* **2004**, 2647-2669; (d) Brown, J. M.; Gridnev, I.;Klankermayer, J. *Top. Curr. Chem.* **2008**, *284,* 35-65; (e) Dimitrov, V.;Kamenova-Nacheva, M. *J. Univ. Chem. Technol. Metall.* **2009**, *44,* 317-332; (f) Erdik, E. *Tetrahedron* **1992**, *48,* 9577-9648; (g) Hatano, M.;Ishihara, K. *Chem. Rec.* **2008**, *8,* 143-155; (h) Komatsu, K.; Wang, G.-W.; Murata, Y.; Mori, S.;Kudo, K. *ICR Annu. Rep.* **1997**, *3,* 32-33; (i) Pu, L. *Chem.--Eur. J.* **1999**, *5,* 2227-2232; (j) Pu, L. *Front. Biotechnol. Pharm.* **2002**, *3,* 325-336; (k) Pu, L.;Yu, H.-B. *Chem. Rev. (Washington, D. C.)* **2001**, *101,* 757-824; (l) Ramon, D. J.;Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43,* 284-287; (m) Ramon, D. J.;Yus, M. *Synlett* **2007**, 2309-2320; (n) Satyanarayana, T.;Kagan, H. B. *Adv. Synth. Catal.* **2005**, *347,* 737-748; (o) Sibi, M. P.;Manyem, S. *Tetrahedron* **2000**, *56,* 8033-8061; (p) Soai, K.;Niwa, S. *Chem. Rev.* **1992**, *92,* 833-856; (q) Soai, K.;Shibata, T. *Yuki Gosei Kagaku Kyokaishi* **1997**, *55,* 994-1005; (r) Yus, M.;Ramon, D. J. *Pure Appl. Chem.* **2005**, *77,* 2111-2119; (s) Yus, M.;Ramon, D. J. *Latv. Kim. Z.* **2007**, 345-353

4 (a) Cartledge, F. K. *J. Organomet. Chem. Libr.* **1981**, *11,* 149-205; (b) Taylor, P. C. *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.* **2009**, *105,* 75-92

5 (a) Miles, W. H.; Duca, D. G.; Freedman, J. T.; Goodzeit, E. O.; Hamman, K. B.; De, S. C. A. P.;Selfridge, B. R. *Heterocycl. Commun.* **2007**, *13,* 195-198; (b) Hayashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77,* 13-21; (c) Delas, C.; Okamoto, S.;Sato, F. *Tetrahedron Lett.* **2002**, *43,* 4373-4375; (d) Chen, H.; Sun, S. Y.;Yu, D. Q. *Chin. Chem. Lett.* **1998**, *9,* 889-892; (e) Zhao, J.; Wang, Y.;Yang, S. *Hecheng Huaxue* **1996**, *4,* 257-260; (f) Kabbara, J.; Flemming, S.; Nickisch, K.; Neh, H.;Westermann, J. *Liebigs Ann.* **1995**, 401-406; (g) Giuliano, R. M.;Villani, F. J., Jr. *J. Org. Chem.* **1995**, *60,* 202-211; (h) Flemming, S.; Kabbara, J.; Nickisch, K.; Neh, H.;Westermann, J. *Tetrahedron Lett.* **1994**, *35,* 6075-6078; (i) Arai, M.; Lipshutz, B. H.;Nakamura, E. *Tetrahedron* **1992**, *48,* 5709-5718; (j) Kawanami, Y.;Katayama, K. *Chem. Lett.* **1990**, 1749-1752; (k) Molander, G. A.;

Burkhardt, E. R.;Weinig, P. *J. Org. Chem.* **1990**, *55,* 4990-4991; (l) Ikeda, Y.; Ukai, J.; Ikeda, N.;Yamamoto, H. *Tetrahedron* **1987**, *43,* 731-741; (m) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R.;Wenderoth, B. *Chem. Ber.* **1985**, *118,* 1441-1454; (n) Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.;Maus, S. *Chem. Ber.* **1985**, *118,* 1421-1440; (o) Reetz, M. T.; Steinbach, R.; Wenderoth, B.;Westmann, J. *Chem. Ind. (London)* **1981**, 541-542; (p) Olivero, A. G.; Weidmann, B.;Seebach, D. *Helv. Chim. Acta* **1981**, *64,* 2485-2488; (q) Carpenter, R. D.;Verkman, A. S. *Org Lett* **2010**, *12,* 1160-1163

6 (a) Arao, T.; Kondo, K.;Aoyama, T. *Tetrahedron Lett.* **2007**, *48,* 4115-4117; (b) Takahashi, G.; Shirakawa, E.; Tsuchimoto, T.;Kawakami, Y. *Chem. Commun. (Cambridge, U. K.)* **2005**, 1459-1461; (c) Hirano, K.; Yorimitsu, H.;Oshima, K. *Org. Lett.* **2005**, *7,* 4689-4691

7 (a) Novodomska, A.; Dudicova, M.; Leroux, F. R.;Colobert, F. *Tetrahedron: Asymmetry* **2007**, *18,* 1628-1634; (b) Lin, S.;Lu, X. *J. Org. Chem.* **2007**, *72,* 9757-9760; (c) Qin, C.; Wu, H.; Cheng, J.; Chen, X. a.; Liu, M.; Zhang, W.; Su, W.;Ding, J. *J. Org. Chem.* **2007**, *72,* 4102-4107; (d) Suzuki, K.; Arao, T.; Ishii, S.; Maeda, Y.; Kondo, K.;Aoyama, T. *Tetrahedron Lett.* **2006**, *47,* 5789-5792; (e) Yamamoto, T.; Ohta, T.;Ito, Y. *Org. Lett.* **2005**, *7,* 4153-4155; (f) Liu, G.;Lu, X. *J. Am. Chem. Soc.* **2006**, *128,* 16504-16505

8 (a) He, P.; Lu, Y.; Dong, C.-G.;Hu, Q.-S. *Org. Lett.* **2007**, *9,* 343-346; (b) He, P.; Lu, Y.;Hu, Q.-S. *Tetrahedron Lett.* **2007**, *48,* 5283-5288

9 (a) Gibson, S.; Foster, D. F.; Cole-Hamilton, D. J.; Eastham, G. R.;Tooze, R. P. *Chem. Commun. (Cambridge, U. K.)* **2001**, 779-780; (b) Nguyen, H. N.; Huang, X.;Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125,* 11818-11819

10 (a) Arao, T.; Suzuki, K.; Kondo, K.;Aoyama, T. *Synthesis* **2006**, 3809-3814; (b) Gois, P. M. P.; Trindade, A. F.; Veiros, L. F.; Andre, V.; Duarte, M. T.; Afonso, C. A. M.; Caddick, S.;Cloke, F. G. N. *Angew. Chem., Int. Ed.* **2007**, *46,* 5750-5753; (c) Jagt, R. B. C.; Toullec, P. Y.; Schudde, E. P.; De, V. J. G.; Feringa, B. L.;Minnaard, A. J. *J. Comb. Chem.* **2007**, *9,* 407-414; (d) Kilincarslan, R.; Yigit, M.; Ozdemir, I.; Cetinkaya, E.;Cetinkaya, B. *J. Heterocycl. Chem.* **2007**, *44,* 69-73; (e) Suzuki, K.; Ishii, S.; Kondo, K.;Aoyama, T. *Synlett* **2006**, 648-650; (f) Yan, C.; Zeng, X.; Zhang, W.;Luo, M. *J. Organomet. Chem.* **2006**, *691,* 3391-3396; (g) Chen, J.; Zhang, X.; Feng, Q.;Luo, M. *J. Organomet. Chem.* **2006**, *691,* 470-474; (h) Duan, H.-F.; Xie, J.-H.; Shi, W.-J.; Zhang, Q.;Zhou, Q.-L. *Org. Lett.* **2006**, *8,* 1479-1481; (i) Oezdemir, I.; Guerbuez, N.; Goek, Y.; Cetinkaya, B.;Cetinkaya, E. *Transition Met. Chem. (Dordrecht, Neth.)* **2005**, *30,* 367-371; (j) Ozdemir, I.; Yigit, M.; Cetinkaya, E.;Cetinkaya, B. *Heterocycles* **2006**, *68,* 1371-1379; (k) Son, S. U.; Kim, S. B.; Reingold, J. A.; Carpenter, G. B.;Sweigart, D. A. *J. Am. Chem.*

*Soc.* **2005**, *127,* 12238-12239; (l) Suzuki, K.; Kondo, K.;Aoyama, T. *Synthesis* **2006**, 1360-1364; (m) Batey, R. A.; Thadani, A. N.;Smil, D. V. *Org. Lett.* **1999**, *1,* 1683-1686; (n) Focken, T.; Rudolph, J.;Bolm, C. *Synthesis* **2005**, 429-436; (o) Fuerstner, A.;Krause, H. *Adv. Synth. Catal.* **2001**, *343,* 343-350; (p) Huang, R.;Shaughnessy, K. H. *Chem. Commun. (Cambridge, U. K.)* **2005**, 4484-4486; (q) Imlinger, N.; Mayr, M.; Wang, D.; Wurst, K.;Buchmeiser, M. R. *Adv. Synth. Catal.* **2004**, *346,* 1836-1843; (r) Moreau, C.; Hague, C.; Weller, A. S.;Frost, C. G. *Tetrahedron Lett.* **2001**, *42,* 6957-6960; (s) Ozdemir, I.; Demir, S.;Cetinkaya, B. *J. Mol. Catal. A: Chem.* **2004**, *215,* 45-48; (t) Tomita, D.; Kanai, M.;Shibasaki, M. *Chem.--Asian J.* **2006**, *1,* 161-166; (u) Ueda, M.;Miyaura, N. *J. Org. Chem.* **2000**, *65,* 4450-4452; (v) Zhang, X.;Larock, R. C. *Org. Lett.* **2005**, *7,* 3973-3976; (w) Aakai, M. U., M.; Miyaura, N. *Angew. Chem. Int. Ed.* **1998**, *37,* 3279-3281; (x) Wada, R.; Oisaki, K.; Kanai, M.;Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126,* 8910-8911

11 (a) Merwin, R. K.; Schnabel, R. C.; Koola, J. D.;Roddick, D. M. *Organometallics* **1992**, *11,* 2972-2978; (b) Pantcheva, I.; Nishihara, Y.;Osakada, K. *Organometallics* **2005**, *24,* 3815-3817; (c) Pantcheva, I.;Osakada, K. *Organometallics* **2006**, *25,* 1735-1741; (d) Suzaki, Y.;Osakada, K. *Organometallics* **2006**, *25,* 3251-3258

12 (a) Bedford, R. B.; Hazelwood, S. L.;Albisson, D. A. *Organometallics* **2002**, *21,* 2599-2600; (b) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E.; Albisson, D. A.; Draper, S. M.; Scully, P. N.; Coles, S. J.;Hursthouse, M. B. *Chem.--Eur. J.* **2003**, *9,* 3216-3227

13 (a) Gini, F.; Hessen, B.;Minnaard, A. J. *Org. Lett.* **2005**, *7,* 5309-5312; (b) Lu, X.;Lin, S. *J. Org. Chem.* **2005**, *70,* 9651-9653; (c) Nishikata, T.; Yamamoto, Y.; Gridnev, I. D.;Miyaura, N. *Organometallics* **2005**, *24,* 5025-5032; (d) Nishikata, T.; Yamamoto, Y.;Miyaura, N. *Chem. Lett.* **2003**, *32,* 752-753; (e) Nishikata, T.; Yamamoto, Y.;Miyaura, N. *Angew. Chem., Int. Ed.* **2003**, *42,* 2768-2770; (f) Nishikata, T.; Yamamoto, Y.;Miyaura, N. *Organometallics* **2004**, *23,* 4317-4324; (g) Nishikata, T.; Yamamoto, Y.;Miyaura, N. *Chem. Lett.* **2005**, *34,* 720-721

14 (a) Chen, F.-X.; Kina, A.;Hayashi, T. *Org. Lett.* **2006**, *8,* 341-344; (b) Hayashi, T.;Yamasaki, K. *Chem. Rev. (Washington, DC, U. S.)* **2003**, *103,* 2829-2844; (c) Shintani, R.; Duan, W.-L.;Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128,* 5628-5629; (d) Trenkle, W. C.; Barkin, J. L.; Son, S. U.;Sweigart, D. A. *Organometallics* **2006**, *25,* 3548-3551; (e) Fagnou, K.;Lautens, M. *Chem. Rev. (Washington, DC, U. S.)* **2003**, *103,* 169-196

15 (a) Xing, C.-H.; Hu, Q.-S. *Tetrahedron Lett.* **2010**, *51,* 924-927; (b) Xing, C.-H.; Liu, T.-P.; Zheng, J. R.; Ng, J.; Esposito, M.;Hu, Q.-S. *Tetrahedron Lett.* **2009**, *50,* 4953-4957

16 Yamamoto, Y.; Kurihara, K.;Miyaura, N. *Angew. Chem., Int. Ed.* **2009**, *48,* 4414-4416

17 Karthikeyan, J.; Jeganmohan, M.;Cheng, C.-H. *Chem. Eur. J.* **2010**, *16,* 8989-8992

18 (a) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.;Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129,* 5336-5337; (b) Wang, Z.-Q.; Feng, C.-G.; Zhang, S.-S.; Xu, M.-H.;Lin, G.-Q. *Angew Chem Int Ed Engl* **2010**, *49,* 5780-5783

19 (a) Zheng, H.; Zhang, Q.; Chen, J.; Liu, M.; Cheng, S.; Ding, J.; Wu, H.;Su, W. *J. Org. Chem.* **2009**, *74,* 943-945; (b) Zou, T.; Pi, S.-S.;Li, J.-H. *Org. Lett.* **2009**, *11,* 453-456

20 Bouffard, J.;Itami, K. *Org. Lett.* **2009**, *11,* 4410-4413

21 Bedford, R. B.; Betham, M.; Charmant, J. P. H.; Haddow, M. F.; Orpen, A. G.; Pilarski, L. T.; Coles, S. J.;Hursthouse, M. B. *Organometallics* **2007**, *26,* 6346-6353

22 (a) Douglas, T. M.; Le, N. J.; Brayshaw, S. K.; Frost, C. G.;Weller, A. S. *Chem. Commun. (Cambridge, U. K.)* **2006**, 3408-3410; (b) Fujita, N.; Motokura, K.; Mori, K.; Mizugaki, T.; Ebitani, K.; Jitsukawa, K.;Kaneda, K. *Tetrahedron Lett.* **2006**, *47,* 5083-5087; (c) Hayashi, T.; Tokunaga, N.; Okamoto, K.;Shintani, R. *Chem. Lett.* **2005**, *34,* 1480-1481; (d) Itooka, R.; Iguchi, Y.;Miyaura, N. *J. Org. Chem.* **2003**, *68,* 6000-6004; (e) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.;Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127,* 10850-10851

23 (a) Lin, T.-C.; Hsu, C.-S.; Hu, C.-L.; Chen, Y.-F.;Huang, W.-J. *Tetrahedron Lett.* **2009**, *50,* 182-185; (b) Nishikata, T.; Yamamoto, Y.;Miyaura, N. *Tetrahedron Lett.* **2007**, *48,* 4007-4010

24 (a) Boschetti, E.; Molho, D.; Chabert, J.; Grand, M.;Fontaine, L. *Chim. Ther.* **1972**, *7,* 20-23; (b) Gunn, D.; Akuche, C.; Baryza, J.; Blue, M.-L.; Brennan, C.; Campbell, A.-M.; Choi, S.; Cook, J.; Conrad, P.; Dixon, B.; Dumas, J.; Ehrlich, P.; Gane, T.; Joe, T.; Johnson, J.; Jordan, J.; Kramss, R.; Liu, P.; Levy, J.; Lowe, D.; McAlexander, I.; Natero, R.; Redman, A. M.; Scott, W.; Seng, T.; Sibley, R.; Wang, M.; Wang, Y.; Wood, J.;Zhang, *Z. Bioorg. Med. Chem. Lett.* **2005**, *15,* 3053-3057

25 (a) Beller, M.;Bolm, C.; *Transition Metals for Organic Synthesis*; Wiley-VCH:

Weinheim, 2004; (b) Collman, J. P.; Hegedus, L. S.; Norton, J. R.;Finke, R. G.; *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; (c) de Meijere, A.;Diederich, F.; *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: New York, 2004

26 (a) Espinet, P.;Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43,* 4704-4734; (b) Osakada, K. *Curr. Methods Inorg. Chem.* **2003**, *3,* 233-291; (c) Partyka, D. V. *Chem. Rev. (Washington, DC, U. S.)* **2011**, *111,* 1529-1595

27 (a) Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43,* 3364-3366; (b) Gutnov, A. *Eur. J. Org. Chem.* **2008**, 4547-4554; (c) Miyaura, N. *Synlett* **2009**, 2039-2050

28 (a) Zhao, P.; Incarvito, C. D.;Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129,* 1876-1877; (b) Yamamoto, T.; Iizuka, M.; Takenaka, H.; Ohta, T.;Ito, Y. *J. Organomet. Chem.* **2009**, *694,* 1325-1332

29 (a) Braga, A. A. C.; Morgon, N. H.; Ujaque, G.;Maseras, F. *J. Am. Chem. Soc.* **2005**, *127,* 9298-9307; (b) Braga, A. A. C.; Ujaque, G.;Maseras, F. *Organometallics* **2006**, *25,* 3647-3658; (c) Glaser, R.;Knotts, N. *J. Phys. Chem. A* **2006**, *110,* 1295-1304; (d) Goossen, L. J.; Koley, D.; Hermann, H. L.;Thiel, W. *J. Am. Chem. Soc.* **2005**, *127,* 11102-11114; (e) Goossen, L. J.; Koley, D.; Hermann, H. L.;Thiel, W. *Organometallics* **2006**, *25,* 54-67

30 (a) Bedford, R. B. *Chem. Commun. (Cambridge, U. K.)* **2003**, 1787-1796; (b) Beletskaya, I. P.;Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689,* 4055-4082; (c) Dupont, J.; Consorti, C. S.;Spencer, J. *Chem. Rev. (Washington, DC, U. S.)* **2005**, *105,* 2527-2571; (d) Newkome, G. R.; Puckett, W. E.; Gupta, V. K.;Kiefer, G. E. *Chem. Rev.* **1986**, *86,* 451-489

31 (a) Liao, Y.-X.; Xing, C.-H.; He, P.;Hu, Q.-S. *Org. Lett.* **2008**, *10,* 2509-2512; (b) Suzuma, Y.; Hayashi, S.; Yamamoto, T.; Oe, Y.; Ohta, T.;Ito, Y. *Tetrahedron: Asymmetry* **2009**, *20,* 2751-2758; (c) Yu, A.; Cheng, B.; Wu, Y.; Li, J.;Wei, K. *Tetrahedron Lett.* **2008**, *49,* 5405-5407

32 Trindade, A. F.; Gois, P. M. P.; Veiros, L. F.; Andre, V.; Duarte, M. T.; Afonso, C. A. M.; Caddick, S.;Cloke, F. G. N. *J. Org. Chem.* **2008**, *73,* 4076-4086

33 (a) Matos, K.;Soderquist, J. A. *J. Org. Chem.* **1998**, *63,* 461-470; (b) Nakai, H.; Ogo,

S.;Watanabe, Y. *Organometallics* **2002**, *21,* 1674-1678; (c) Retboll, M.; Edwards, A. J.; Rae, A. D.; Willis, A. C.; Bennett, M. A.;Wenger, E. *J. Am. Chem. Soc.* **2002**, *124,* 8348-8360

34 (a) Bouffard, J.;Itami, K. *Org. Lett.* **2009**, *11,* 4410-4413; (b) Miyamura, S.; Satoh, T.;Miura, M. *J. Org. Chem.* **2007**, *72,* 2255-2257; (c) Ueura, K.; Miyamura, S.; Satoh, T.;Miura, M. *J. Organomet. Chem.* **2006**, *691,* 2821-2826

35 Ohmiya, H.; Yoshida, M.;Sawamura, M. *Org. Lett.* **2011**, *13,* 482-485

36 Takatsu, K.; Shintani, R.;Hayashi, T. *Angew. Chem., Int. Ed.* **2011**, *50,* 5548-5552, S5548/5541-S5548/5115

37 Xing, C.-H.; Liao, Y.-X.; He, P.;Hu, Q.-S. *Chem. Commun. (Cambridge, U. K.)* **2010**, *46,* 3010-3012

38 (a) Kuriyama, M.; Ishiyama, N.; Shimazawa, R.; Shirai, R.;Onomura, O. *J. Org. Chem.* **2009**, *74,* 9210-9213; (b) Kuriyama, M.; Shimazawa, R.; Enomoto, T.;Shirai, R. *J. Org. Chem.* **2008**, *73,* 6939-6942; (c) Kuriyama, M.; Shimazawa, R.;Shirai, R. *J. Org. Chem.* **2008**, *73,* 1597-1600; (d) Lin, S.;Lu, X. *Tetrahedron Lett.* **2006**, *47,* 7167-7170; (e) Liu, G.;Lu, X. *Tetrahedron* **2008**, *64,* 7324-7330; (f) Nishikata, T.; Kiyomura, S.; Yamamoto, Y.;Miyaura, N. *Synlett* **2008**, 2487-2490

39 Karthikeyan, J.; Jeganmohan, M.;Cheng, C.-H. *Chem.--Eur. J.* **2010**, *16,* 8989-8992, S8989/8981-S8989/8950

40 (a) Bolm, C.;Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124,* 14850-14851; (b) Matsuda, T.; Makino, M.;Murakami, M. *Org. Lett.* **2004**, *6,* 1257-1259; (c) Shintani, R.; Inoue, M.;Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45,* 3353-3356

41 (a) Tuerkmen, H.; Denizalti, S.; Oezdemir, I.; Cetinkaya, E.;Cetinkaya, B. *J. Organomet. Chem.* **2008**, *693,* 425-434; (b) Jia, X.; Fang, L.; Lin, A.; Pan, Y.;Zhu, C. *Synlett* **2009**, 495-499; (c) Zhou, L.; Du, X.; He, R.; Ci, Z.;Bao, M. *Tetrahedron Lett.* **2009**, *50,* 406-408

42 (a) Nicolaou, K. C.; Montagnon, T.;Snyder, S. A. *Chem. Commun. (Cambridge, U. K.)* **2003**, 551-564; (b) Parsons, P. J.; Penkett, C. S.;Shell, A. J. *Chem. Rev. (Washington, D.*

*C.)* **1996**, *96,* 195-206; (c) Tietze, L. F. *Chem. Rev. (Washington, D. C.)* **1996**, *96,* 115-136; (d) Tietze, L. F.;Rackelmann, N. *Pure Appl. Chem.* **2004**, *76,* 1967-1983

43 (a) Deng, Y.; Chin, Y.-W.; Chai, H.; Keller, W. J.;Kinghorn, A. D. *J. Nat. Prod.* **2007**, *70,* 2049-2052; (b) Iijima, D.; Tanaka, D.; Hamada, M.; Ogamino, T.; Ishikawa, Y.;Nishiyama, S. *Tetrahedron Lett.* **2004**, *45,* 5469-5471; (c) Katoh, T.; Ohmori, O.; Iwasaki, K.;Inoue, M. *Tetrahedron* **2002**, *58,* 1289-1299; (d) Pecchio, M.; Solis, P. N.; Lopez-Perez, J. L.; Vasquez, Y.; Rodriguez, N.; Olmedo, D.; Correa, M.; San, F. A.;Gupta, M. P. *J. Nat. Prod.* **2006**, *69,* 410-413; (e) Storm, J. P.;Andersson, C.-M. *J. Org. Chem.* **2000**, *65,* 5264-5274

44 (a) Chuzel, O.; Roesch, A.; Genet, J.-P.;Darses, S. *J. Org. Chem.* **2008**, *73,* 7800-7802; (b) Mora, G.; Darses, S.;Genet, J.-P. *Adv. Synth. Catal.* **2007**, *349,* 1180-1184; (c) Pucheault, M.; Darses, S.;Genet, J.-P. *J. Am. Chem. Soc.* **2004**, *126,* 15356-15357; (d) Qin, C.; Chen, J.; Wu, H.; Cheng, J.; Zhang, Q.; Zuo, B.; Su, W.;Ding, J. *Tetrahedron Lett.* **2008**, *49,* 1884-1888

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

46 (a) Buergi, J. J.; Mariz, R.; Gatti, M.; Drinkel, E.; Luan, X.; Blumentritt, S.; Linden, A.;Dorta, R. *Angew. Chem., Int. Ed.* **2009**, *48,* 2768-2771; (b) Chen, J.; Chen, J.-M.; Lang, F.; Zhang, X.-Y.; Cun, L.-F.; Zhu, J.; Deng, J.-G.;Liao, J. *J. Am. Chem. Soc.* **2010**, *132,* 4552-4553; (c) Chen, Q.; Kuriyama, M.; Hao, X.; Soeta, T.; Yamamoto, Y.; Yamada, K.-i.;Tomioka, K. *Chem. Pharm. Bull.* **2009**, *57,* 1024-1027; (d) Drinkel, E.; Briceno, A.; Dorta, R.;Dorta, R. *Organometallics* **2010**, *29,* 2503-2514; (e) Facchetti, S.; Cavallini, I.; Funaioli, T.; Marchetti, F.;Iuliano, A. *Organometallics* **2009**, *28,* 4150-4158; (f) Hahn, B. T.; Tewes, F.; Froehlich, R.;Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49,* 1143-1146, S1143/1141-S1143/1170; (g) Hu, X.; Cao, Z.; Liu, Z.; Wang, Y.;Du, H. *Adv. Synth. Catal.* **2010**, *352,* 651-655; (h) Iuliano, A.; Facchetti, S.;Funaioli, T. *Chem. Commun. (Cambridge, U. K.)* **2009**, 457-459; (i) Jana, R.;Tunge, J. A. *Org. Lett.* **2009**, *11,* 971-974; (j) Jeletic, M. S.; Ghiviriga, I.; Abboud, K. A.;Veige, A. S. *Dalton Trans.* **2010**, *39,* 6392-6394; (k) Kim, S. B.; Cai, C.; Faust, M. D.; Trenkle, W. C.;Sweigart, D. A. *Organometallics* **2009**, *28,* 2625-2628; (l) Korenaga, T.; Osaki, K.; Maenishi, R.;Sakai, T. *Org. Lett.* **2009**, *11,* 2325-2328; (m) Lang, F.; Li, D.; Chen, J.; Chen, J.; Li, L.; Cun, L.; Zhu, J.; Deng, J.;Liao, J. *Adv. Synth. Catal.* **2010**, *352,* 843-846; (n) Minuth, T.;Boysen, M. M. K. *Org. Lett.* **2009**, *11,* 4212-4215; (o) Nishimura, T.; Yasuhara, Y.; Sawano, T.;Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132,* 7872-7873; (p) Wallace, G. A.; Gordon, T. D.; Hayes, M. E.; Konopacki, D. B.; Fix-Stenzel, S. R.; Zhang, X.; Grongsaard, P.; Cusack, K. P.; Schaffter, L. M.; Henry, R. F.;Stoffel, R. H. *J. Org. Chem.* **2009**, *74,* 4886-4889; (q) Yuan, W.-C.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.;Gong, L.-Z. *Tetrahedron*

**2009**, *65,* 4130-4141

47 Liao, Y.-X.;Hu, Q.-S. *J. Org. Chem.* **2010**, *75,* 6986-6989

48 (a) Bocknack, B. M.; Wang, L.-C.;Krische, M. J. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101,* 5421-5424; (b) Cauble, D. F.; Gipson, J. D.;Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125,* 1110-1111; (c) Navarro, C.;Csaky, A. G. *Synthesis* **2009**, 860-863; (d) Navarro, C.;Csakye, A. G. *Org. Lett.* **2008**, *10,* 217-219; (e) Nishikata, T.; Kobayashi, Y.; Kobayshi, K.; Yamamoto, Y.;Miyaura, N. *Synlett* **2007**, 3055-3057; (f) Youn, S. W.; Song, J.-H.;Jung, D.-I. *J. Org. Chem.* **2008**, *73,* 5658-5661

49 (a) Hayashi, T.; Takahashi, M.; Takaya, Y.;Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124,* 5052-5058; (b) Takada, Y.; Hayashi, S.; Hirano, K.; Yorimitsu, H.;Oshima, K. *Org. Lett.* **2006**, *8,* 2515-2517

50 Sakai, M.; Ueda, M.;Miyaura, N. *Angew. Chem., Int. Ed.* **1998**, *37,* 3279-3281

51 Duan, H.-F.; Xie, J.-H.; Qiao, X.-C.; Wang, L.-X.;Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2008**, *47,* 4351-4353