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Cationic Palladium Complex Catalyzed Highly Enantioselective Intramolecular Addition of Arylboronic Acids to Ketones. A Convenient Synthesis of Optically Active Cycloalkanols

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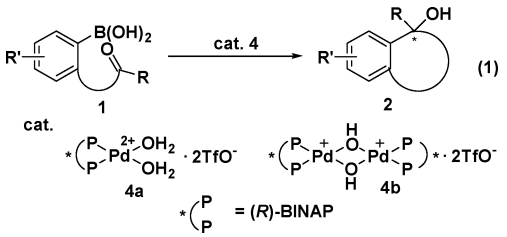
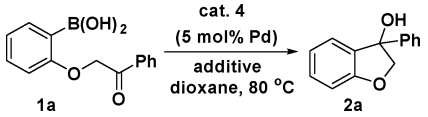
Enantioselective addition of organometallic reagents to ketones is a straightforward strategy for the construction of optically active tertiary alcohols.[1] While there are many reports in the enantioselective addition of alkyl or aryl groups to aldehydes,[2] fewer catalyst systems will promote the analogous addition reactions to ketones owing to its attenuated reactivity.[1,3] As to the enantioselective arylation of ketones, much success has been achieved by using arylzinc reagents.[1,4] However, when considering the availability and stability of the substrate sources, arylboronic acid is a promising alternative arylating reagent.[1b] This makes transition-metal-catalyzed asymmetric addition of arylboronic acids to ketones useful and attractive, though successful examples of this type reaction are still rare.[5,6] Recently, Hayashi and de Vries independently reported the first example of Rh-catalyzed asymmetric addition of arylboronic acids to α-dicarbonyl substrates, isatins.[7] To the best of our knowledge, there have been no reports for the enantioselective addition of arylboronic acids to simple ketones catalyzed by palladium.[8−10]

The nonasymmetric arylation of ketones has been achieved in Pd(0)-catalyzed intramolecular nucleophilic addition of aryl halides to ketones reported by Yamamoto and others.[9] In these reactions, a Pd(II) species was formed after quenching an oxygen-palladium bond. It occurred to us that if a Pd(II) complex was used as the catalyst in this addition reaction, the catalyst system will be simplified without the use of a redox system.[11] Among kinds of Pd(II) catalysts, cationic Pd(II) complexes have great advantages over analogous neutral ones mainly in two dimensions: (1) vacant coordination site for substrates or reagents and (2) stronger Lewis acidity.[12] We describe herein the application of the chiral cationic palladium complex as a catalyst in the asymmetric intramolecular addition of arylboronic acids to ketones (eq 1) for the highly enantioselective synthesis of cycloalkanols.



Initially, we chose cationic palladium complex $[Pd(dppp)(H_2O)_2]^{2+}(OTf^-)_2$ (**3a**)[13] as the catalyst to examine the intramolecular 1,2-addition of **1a**. Fortunately, upon heating at 80 °C for 1 h in the presence of 2 equiv of K_3PO_4, 2 equiv of H_2O, and 5 mol % of **3a** in dioxane, **1a** underwent addition smoothly to afford dihydrobenzofuranol **2a** in high yield (91%).[14] No addition product will be obtained in the absence of palladium catalyst. We then turned our efforts on the asymmetric version of this addition reaction using the easily prepared chiral cationic palladium complex **4a** and **4b**[15] as the catalyst. However, with the catalysis of **4a** under the optimized reaction conditions, **2a** was formed in high yield (89%) with extremely low ee (7%; Table 1, entry 1). When chiral Pd complex **4b** was used instead of **4a**, a slight improvement in the ee value was observed (28%; Table 1, entry 2). Lowering the amount of K_3PO_4 from 2 equiv to 0.5 equiv led to significant enhancement in enantioselectivity (51%; Table 1, entry 3). Surprisingly, a dramatic improvement in enantioselectivity was obtained in the absence of a base though the yield was not satisfied (49% yield, 85% ee; Table 1, entry 4). These prompted us to seek for a suitable base which may have enough basicity[14] to maintain both high yield and enantioselectivity. To our delight, while employing anion exchange resin (Amberlite IRA 400 (OH)) as the additive, we effectively furnished the cyclization product **2a** in good yield with high enantiomeric excess (85% yield, 82% ee; Table 1, entry 5). The solvent and temperature effects were also examined. Finally, it turned out that a **4b**/Amberlite IRA-400(OH) combination in toluene at 40 °C provided the best result (85% yield, 91% ee; Table 1, entry 6).

Table 1. Optimization of Asymmetric Reaction Conditions



entry	additive (equiv)	time (h)	yield[a]/ee[b] (%/%)
1[c]	K_3PO_4 (2), H_2O (2)	1	89/7
2[d]	K_3PO_4 (2), H_2O (2)	1	77/ 28
3[d]	K_3PO_4 (0.5)	2	83/51
4[d]	None	1	49/85
5[d]	Amberlite IRA−400 (OH) (1.5)	2	85/82
6[d,e]	Amberlite IRA−400 (OH) (1.5)	12	85/92

[a] Isolated yield. [b] Determined by HPLC analysis using a Chiralcel OD column. [c] **4a** was used as the catalyst. [d] **4b** was used as the catalyst. [e] Toluene was used as the solvent and the reaction temperature was 40 °C.

A variety of substrates[16] including various aromatic, heteroaromatic, and aliphatic ketones could be used to afford the optically active tertiary alcohols in good to excellent yield and high enantioselectivity under very mild conditions (Table 2, entries 1−6). Substituents on the arylboronic acids did not affect the additon reaction too much (Table 2, entries 7−9). Derivatives of indan and chroman could also be formed smoothly in moderate yields and enantioselectivity. (Table 2, entries 10 and 11). A comparable low enantioselectivity was observed for the formation of six-membered ring product (Table 2, entry 11).

A plausible mechanism for the asymmetric arylation of ketones is shown in Scheme 1. Cationic palladium complex **4b** is in equilibrium with the Pd hydroxo complex **A**,[15c] which enable smooth transmetalation with the substrate. Two features of intermediate **A** may account for its feasible transmetalation: the cationic nature of

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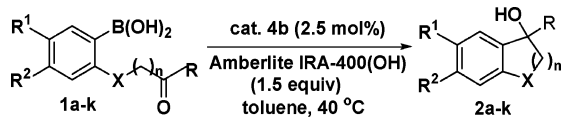
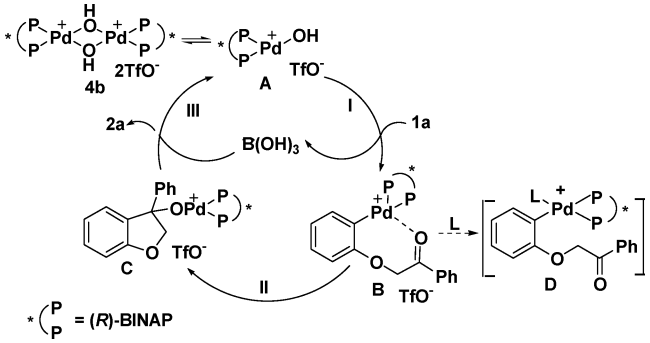
Table 2. Chiral Cationic Palladium Complex **4b** Catalyzed Enantioselective Intramolecular Addition of Arylboronic Acids to Ketones[a]



entry	substrate	product	yield (%)[b]	ee (%)[c]
	X = O, n = 1, $R^1 = R^2$ = H			
1	**1a**: R = Ph	**2a**	85	92 (−)
2[d]	**1b**: R = 4-$MeOC_6H_4$	**2b**	92	91 (−)
3[d]	**1c**: R = 4-ClC_6H_4	**2c**	90	87 (−)
4[d]	**1d**: R = 4-$CF_3C_6H_4$	**2d**	86	93 (−)
5[d,f]	**1e**: R = 2-furyl	**2e**	84	84 (−)
6	**1f**: $R = CH_3$	**2f**	58	96 (−)
	X = O, n = 1, R = Ph			
7[d]	**1g**: R^1 = H, R^2 = OMe	**2g**	91	89 (−)
8[d]	**1h**: R^1 = Cl, R^2 = H	**2h**	83	89 (−)
9[d]	**1i**: $R^1 = CH_3$, R^2 = H	**2i**	82	93 (−)
	X = CH_2, n = 1, R = Ph			
10[e]	**1j**: $R^1 = R^2$ = H	**2j**	53	66 (−)[g]
	X = O, n = 2, R = Ph			
11[d]	**1k**: $R^1 = R^2$ =H	**2k**	82	53 (−)

[a] Unless otherwise indicated, all reactions were performed at 40 °C using the substrate (0.2 mmol), Amberlite IRA-400 (OH) (1.5 eqiuv), and **4b** (2.5 mol %) in toluene (2 mL) under N_2. [b] Isolated yield. [c] Determined by HPLC analysis using a Chiralcel OD column. The sign of optical rotation was indicated in parentheses. [d] Using toluene/dioxane (1:1) as solvent. [e] Using toluene/DCE (1:1) as solvent. [f] Reaction temperature was 80 °C. [g] The absolute configuration was determined to be (*R*) (see Supporting Information).

Scheme 1. Plausible Mechanism for the Enantioselective Intramolecular Addition of Arylboronic Acids to Ketones Catalyzed by a Cationic Pd(II) Complex **4b**



the transition-metal complex and the hydroxo ligand.[17] After transmetalation (step I), arylpalladium species **B** undergoes intramolecular 1,2-addition (step II) to the ketone to form addition product **C**, which upon hydrolysis (step III) forms product **2a** and regenerates the catalytic active intermediate **A**. High Lewis acidity of the palladium center in cationic species **B** may activate the carbonyl group by coordination making the addition reactions easy to occur.[12] It is also proposed that this coordinated intermediate **B** is helpful to the enantioface discrimination of ketones resulting in high ee values.[1a] When the reaction is carried out in the presence of a coordinative solvent such as MeOH, or DMF, a competitive intermediate **D**, which is more conformationally flexible, will produce the low ee value. These results indicate the dual role of the cationic palladium complex in the catalytic cycle: it acts as the transition metal in step I and plays the role of Lewis acid in step II.[18]

In summary, a highly enantioselective synthesis of optically active cycloalkanols by utilizing the chiral cationic palladium complex **4b** as catalyst was achieved. Further studies on probing the detailed mechanism and expanding the intermolecular reactions are currently underway.

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Supporting Information Available: Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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