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Asymmetric 1,4-Addition of Arylboronic Acids to 2,3-Dihydro-4-pyridones Catalyzed by Axially Chiral NHC−Pd(II) Complexes

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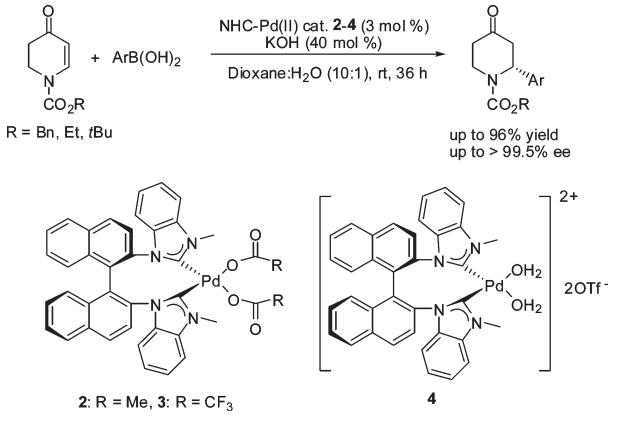

Axially chiral cis-chelated bidentate bis(*N*-heterocyclic carbene)−palladium(II) complexes are effective catalysts for the asymmetric conjugate addition of arylboronic acids to 2,3-dihydro-4-pyridones, producing the synthetically and biologically important 2-aryl-4-piperidones in moderate-to-high yields (up to 96%) along with excellent enantioselectivities (up to > 99.5% ee) in most cases under mild conditions.

The asymmetric conjugate addition of organometallic reagents to Michael acceptors is one of the most useful methods for the construction of chiral C−C bonds.[1] These addition reactions have been used as key steps in the synthesis of numerous biologically active compounds.[2] The piperidine ring is a key unit in many natural products, biologically active molecules, and drugs.[3] Piperidones serve a role as advanced intermediates to piperidines.[4] They are also attractive synthetic targets due to their interesting pharmacological properties.[5] Thus far, numerous asymmetric synthetic routes have been developed for preparation of substituted piperidones and piperidines, and many efforts have been devoted to make short, versatile, stereocontrolled routes for the synthesis of these compounds.[4e,f,6] Enantioselective conjugate addition to readily accessible N-substituted 2,3-dihydro-4-pyridones[7] is an attractive catalytic route toward enantiopure piperidones. However, to the best of our knowledge, only a few suitable procedures, with the exception of the elegant works of Hayashi et al. and Vries et al. have been reported.[8]

N-Heterocyclic carbenes (NHC) have become a very important class of ligands in transition metal catalysis due to their stability to air and in some cases to moisture, and their strong σ-donor but poor π-acceptor abilities.[9] Previously,

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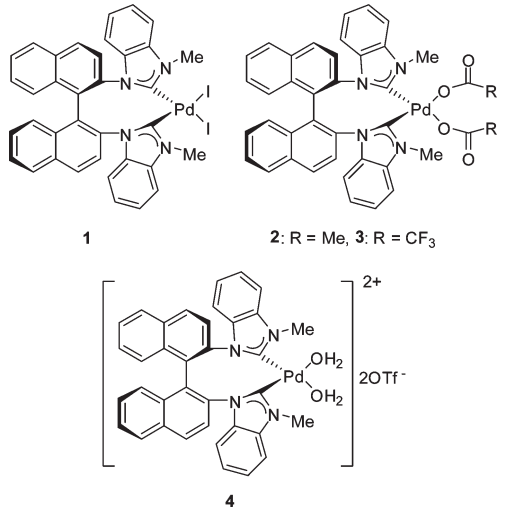


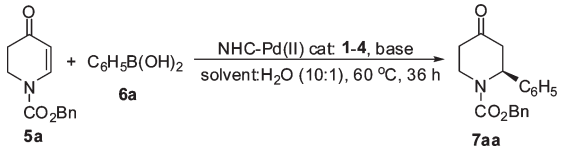
FIGURE 1. The structure of NHC−Pd(II).

our research group has synthesized a series of axially chiral bis(NHC) palladium complexes derived from 1,1′-binaphthalenyl-2,2′-diamine (BINAM) and H_8-BINAM, and successfully applied them in several asymmetric catalytic reactions.[10] To further explore the applications of this kind of axially chiral bis(NHC)−Pd(II) complexes, here we report an interesting example of the asymmetric conjugate addition of arylboronic acids to N-substituted 2,3-dihydro-4-pyridones catalyzed by axially chiral cis-chelated bidentate bis(NHC)−palladium(II) complexes **1**−**4** (Figure 1).

Asymmetric conjugate addition of $PhB(OH)_2$ **6a** to 2,3-dihydro-4-pyridones **5a** with use of NHC−Pd(II) complex **3** was selected as the model reaction to seek optimal reaction conditions. The results are summarized in Table 1. We initiated our investigation by screening a series of bases and solvents and found that 1,4-dioxane is the best solvent and KOH is the preferred base to give the desired product **7aa** in 90% yield along with an excellent ee (>99.5% ee) within 36 h at 60 °C (Table 1, entries 5−12). Lowering the reaction temperature to 15 °C, the yield of **7aa** was rather low (Table 1, entry 14). Elevating the reaction temperature to 100 °C, the yield and the ee value of **7aa** slightly decreased. Encouraged by this excellent result (Table 1, entry 3), bis(NHC)−Pd(II) complexes **1**, **2**, and **4** were examined under identical conditions. Delightfully, it was found that the use of chiral cationic NHC−Pd^{2+} diaquo complex **4** as the catalyst led to the adduct **7aa** in 88% yield along with an excellent ee of >99.5% (Table 1, entry 4). In the presence of bis(NHC)−Pd(II) complex **2**, adduct **7aa** was obtained in 86% yield and 99.3% ee. However, bis(NHC)−Pd(II) complex **1** was ineffective in this reaction (Table 1, entry 1).

Having identified these optimal reaction conditions, the generality of this interesting asymmetric conjugate addition reaction was examined with NHC−Pd(II) complexes **3** and **4** as catalysts, and the results are summarized in Table 2. The asymmetric conjugate addition of a variety of arylboronic acids **6b**−**g** having diverse substituents on the benzene rings was evaluated for the reaction with **5a** under the standard conditions. The adducts **7ab**−**ag** were obtained in good yields (72−96%) along with excellent enantioselectivities

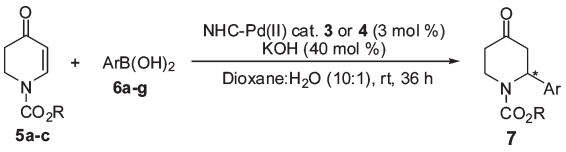
TABLE 1. Optimization of Reaction Conditions



entry	Pd cat.	solvent	base	yield[a](%)	ee (%)[b,c]
1	**1**	dioxane	KOH	<5	n.d.
2	**2**	dioxane	KOH	86	99.3 (*S*)
3	**3**	dioxane	KOH	88	>99.5 (*S*)
4	**4**	dioxane	KOH	88	>99.5(*S*)
5	**3**	DCM	KOH	65	98.6 (*S*)
6	**3**	DMSO	KOH	15	91.9 (*S*)
7	**3**	toluene	KOH	75	98.1 (*S*)
8	**3**	hexane	KOH	26	77.9 (*S*)
9	**3**	dioxane	Cs_2CO_3	56	98.5 (*S*)
10	**3**	dioxane	KF	40	95.9 (*S*)
11	**3**	dioxane	Na_2CO_3	45	97.6 (*S*)
12	**3**	dioxane	KOtBu	56	96.8 (*S*)
13[d]	**3**	dioxane	KOH	80	99.1 (*S*)
14[e]	**3**	dioxane	KOH	60	98.5 (*S*)

[a]Isolated yields. [b]The ee value was determined by HPLC, using a Chiralcel OD-H column. [c]The absolute configuration of **7aa** was determined by comparing the optical rotation $[\alpha]_D$ with the data in the literature. [d]The reaction temperature was 100 °C. [e]The reaction temperature was 15 °C.

TABLE 2. Asymmetric Conjugation of Addition of Arylboron Acids to 2,3-Dihydro-4-pyridones[a]



entry	Pd cat.	R	Ar	yield of **7** (%)[b]	ee of **7** (%)[c,d]
1	**3**	Bn (**5a**)	4-$CH_3C_6H_4$ (**6b**)	85 (**7ab**)	96 (*S*)
2	**4**	Bn (**5a**)	4-$CH_3C_6H_4$ (**6b**)	82 (**7ab**)	95 (*S*)
3	**3**	Bn (**5a**)	3-$CH_3C_6H_4$ (**6c**)	80 (**7ac**)	95 (*S*)
4	**4**	Bn (**5a**)	3-$CH_3C_6H_4$ (**6c**)	80 (**7ac**)	98 (*S*)
5	**3**	Bn (**5a**)	4-$CH_3OC_6H_4$ (**6d**)	78 (**7ad**)	>99.5 (*S*)
6	**4**	Bn (**5a**)	4-$CH_3OC_6H_4$ (**6d**)	82 (**7ad**)	>99.5 (*S*)
7	**3**	Bn (**5a**)	3-$CH_3OC_6H_4$ (**6e**)	76 (**7ae**)	99 (−)
8	**4**	Bn (**5a**)	3-$CH_3OC_6H_4$ (**6e**)	72 (**7ae**)	90 (−)
9	**3**	Bn (**5a**)	2-naphthyl (**6f**)	85 (**7af**)	98 (−)
10	**4**	Bn (**5a**)	2-naphthyl (**6f**)	86 (**7af**)	97 (−)
11	**3**	Bn (**5a**)	4-$C_6H_5C_6H_4$ (**6g**)	94 (**7ag**)	97 (*S*)
12	**4**	Bn (**5a**)	4-$C_6H_5C_6H_4$ (**6g**)	96 (**7ag**)	98 (*S*)
13	**3**	Et (**5b**)	C_6H_5 (**6a**)	92 (**7ba**)	87 (−)
14	**4**	Et (**5b**)	C_6H_5 (**6a**)	90 (**7ba**)	98 (−)
15	**3**	Et (**5b**)	2-naphthyl (**6f**)	85 (**7bf**)	97 (−)
16	**3**	Et (**5b**)	4-$C_6H_4C_6H_4$ (**6g**)	95 (**7bg**)	97 (−)
17	**3**	^{t}Bu (**5c**)	C_6H_5 (**6a**)	82 (**7ca**)	99 (−)
18	**4**	^{t}Bu (**5c**)	C_6H_5 (**6a**)	80 (**7ca**)	98 (−)
19	**3**	^{t}Bu (**5c**)	2-naphthyl (**6f**)	80 (**7cf**)	97 (−)
20	**3**	^{t}Bu (**5c**)	4-$C_6H_5C_6H_4$ (**6g**)	95 (**7cg**)	>99.5 (−)

[a]All reactions were conducted with **5** (0.25 mmol), **6** (0.75 mmol), KOH (0.1 mmol), and NHC−Pd^{II} catalyst **3** or **4** (0.0075 mmol) in dioxane/H_2O (10/1, 1.1 mL) at 60 °C for 36 h. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]The absolute configurations were determined by comparing the optical rotation with those of known data.

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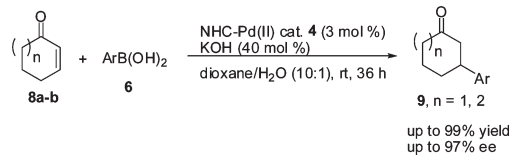
SCHEME 1. NHC−Pd^{2+} Diaquo Complex 4 in the Asymmetric Conjugate Addition of Arylboronic Acids to Cycloaliphatic Enones



(90% to >99.5% ee) (Table 2, entries 1−12). By using other N-substituted 2,3-dihydro-4-pyridones **5b** and **5c** as the substrates to react with arylboronic acids **6a**, **6f**, and **6g**, the corresponding adducts were produced in good yields (72−96%) and high enantiomeric excesses (90% to >99.5% ee) in the presence of catalyst **3** or **4** under the optimized conditions (Table 2, entries 13−20). These results indicated that the various N-substituents of 2,3-dihydro-4-pyridones do not significantly affect the reactivities and enantioselectivities of the 1,4-additions. Generally speaking, chiral NHC−Pd(II) complex **3** and cationic NHC−Pd^{2+} diaquo complex **4** gave the corresponding 2-aryl-4-piperidones **7** in similar enantioselectivities and chemical yields under identical reaction conditions. It should also be noted that using benzyl group (Bn) as a protecting group did not give the corresponding addition product and employing vinylboronic acid afforded the product in <10% ee under the standard conditions.

In view of the above results, we envisioned that chiral cationic NHC−Pd^{2+} diaquo complex **4** might also show similar asymmetric activities as those of NHC−Pd(II) complexes **2** and **3** in the asymmetric conjugate addition of arylboronic acids to other cyclic enones.[10d] To test our hypothesis, asymmetric conjugate addition of ArB(OH)$_2$ **6** to cyclic enones **8** with chiral cationic NHC−Pd^{2+} diaquo complex **4** was investigated. It was found that complex **4** showed excellent catalytic activities and enantioselectivities with up to 99% yield and up to 97% ee (Scheme 1).[11] The details of these results was summarized in the Supporting Information.

In conclusion, we have developed an effective axially chiral bis(NHC)−Pd-catalyzed asymmetric conjugate addition of arylboronic acids to N-substituted 2,3-dihydro-4-pyridones, which affords the corresponding adducts in good-to-high yields along with high-to-excellent enantioselectivities in most cases under mild conditions. Efforts to explore this catalytic system in other asymmetric C−C bond-forming reactions and to optimize the structure of the bis(NHC)−Pd complexes are underway.

(11) Chiral cationic NHC−Pd^{2+} diaquo complex **4** was also applied in the asymmetric conjugate addition of arylboronic acids to cycloaliphatic enones **8a**,**b**, affording adducts **9** in good yields and high ee values (see the Supporting Information).

Experimental Section

General Procedure for Chiral NHC−Palladium-Catalyzed Conjugate Addition of Arylboronic Acids to 2,3-Dihydro-4-pyridones. In a flame-dried Schlenk tube equipped with septum cap and stirring bar, NHC−Pd(II) complex (3 mol %, 0.0075 mmol) and KOH (40 mol %, 0.1 mmol, 5.6 mg) were dissolved in dry dioxane (1.0 mL) and stirred under argon at room temperature for 10 min. Arylboronic acid **6** (1.5 equiv, 0.375 mmol) was added, followed by the addition of 2,3-dihydro-4-pyridone **5** (0.25 mmol). After the addition of H_2O (0.1 mL), the reaction mixture was stirred at 60 °C for 36 h. Saturated aqueous $NaHCO_3$ solution was added. The organic phase was separated and the resulting aqueous layer was extracted with Et_2O. The combined organic phases were filtered through a plug of silica, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash chromatography (eluent: EA/PE) to yield the corresponding product **7**.

(−)-2-(3-Methoxyphenyl)-4-oxo-piperidine-1-carboxylic acid benzyl ester (7ae): colorless liquid; $[\alpha]^{20}_D$ −107.2 (*c* 1.26, $CHCl_3$); IR (CH_2Cl_2) ν 2924, 1697, 1600, 1585, 1491, 1418, 1241, 785, 766, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 2.35−2.39 (m, 1H), 2.48−2.57 (m, 1H), 2.84 (dd, J = 6.8, 15.6 Hz, 1H), 2.97 (d, J = 15.6 Hz, 1H), 3.22 (t, J = 14.0 Hz, 1H), 3.74 (s, 3H), 4.27 (br, 1H), 5.17−5.29 (m, 2H), 5.79 (br, 1H), 6.78−6.83 (m, 3H), 7.21−7.26 (m, 1H), 7.32−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS) δ 207.1, 159.9, 155.4, 141.4, 136.2, 129.8, 128.5, 128.2, 128.0, 118.8, 111.1, 112.5, 67.7, 55.1, 54.5, 44.2, 40.5, 38.9; MS (EI) m/z 339.1 (M$^+$, 4.96), 248.1 (100), 204.1 (74.6), 162.1 (45.8), 91.1 (66.6); HRMS (EI) calcd for $C_{20}H_{21}NO_4$ requires 339.1471, found 339.1472.

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Supporting Information Available: Detailed description of experimental procedures and full characterization of new compounds shown in the tables and figures. This material is available free of charge via the Internet at http://pubs.acs.org.