Pd(*N*,*N*-Dimethyl β-alaninate)$_2$ as a High-Turnover-Number, Phosphine-Free Catalyst for the Suzuki Reaction

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Received 25 August 2006; revised 12 October 2006

Abstract: A novel crystalline, air- and moisture-stable Pd salt, Pd(*N*,*N*-dimethyl β-alaninate)$_2$, was synthesized. This salt was demonstrated to constitute a low-priced, phosphine-free, yet high-turnover-number (TON = 10^4) catalyst for the Suzuki reactions of various aryl bromides and iodides under mild and simple reaction conditions. Moreover, it was observed that the presence of an olefin could dramatically hamper the Suzuki reaction.

Key words: palladium, Suzuki reaction, phosphine-free ligand, high-turnover-number catalyst

The Pd-catalyzed cross coupling of aryl and alkenyl halides with organoboronic acids is known as the Suzuki reaction.[1] This reaction, normally performed with 1–5 mol% of Pd along with phosphine ligands, has become one of the most versatile methods for the C–C bond formation in organic synthesis. The Suzuki reaction has been successfully utilized in the synthesis of a wide variety of valuable compounds including pharmaceuticals, natural products, and functional organic materials. Despite these successes, large-scale industrial applications of the Suzuki reaction are still limited mainly due to the following two problems.[2] First, Pd is expensive and contamination of the product by Pd has to be tightly controlled. Second, and perhaps more limiting is that many phosphine ligands are more expensive than Pd and are not pleasant to work with, because they are toxic, air-sensitive, and difficult to recycle. Accordingly, one of the current challenges in the field is the development of high-turnover-number catalysts (HTC)[3] that utilize inexpensive and non-phosphine ligands.

To meet the challenge, a number of phosphine-free catalysts have been examined for the Suzuki reaction. Previously studied ligands included heterocyclic carbenes,[4] oxazolines,[5] oximines,[6] imines,[7] diazabutadienes,[8] simple amines,[9] bispyridines,[10] hydrazones,[11] pyrazoles,[12] and surfactants.[13] Good to excellent yields were usually reported for these ligands in the Suzuki reaction, which strongly suggested the promising application of the non-phosphine ligands in the Pd catalysis. Nonetheless, two problems have to be pointed out for the previously reported phosphine-free ligands: (1) most of these phosphine-free ligands are not commercially available and some are cumbersome to synthesize; and (2) in most of the above studies the Pd/ligand loading was higher than 1 mol% and therefore, the corresponding catalyst could not be considered as a HTC. Due to these two problems, further studies on the use of non-phosphine ligands in the Suzuki reaction are still highly warranted, where the key challenge is how to achieve high turnover numbers without employing any expensive ligand.

Herein we wish to report that a well-defined Pd(II) salt of *N*,*N*-dimethyl β-alaninate is an inexpensive, yet highly efficient catalyst for the Suzuki reaction. This work is part of our continuing efforts to investigate how to use more economically competitive metals (e.g. Fe, Co, Ni, and Cu) and/or ligands (in particular, phosphine-free ligands) to accomplish the traditional Pd-catalyzed reactions.[14] Previously we reported that the combination of Pd(OAc)$_2$ and the *N*,*N*-dimethyl β-alanine ligand constituted an efficient catalytic system for the Heck reaction of aryl bromides.[15] After the study was completed for some time, it was discovered unexpectedly that some nice single crystals were produced in the mother liquor left of the mixture of Pd(OAc)$_2$ and *N*,*N*-dimethyl β-alanine. Through X-ray measurements it was determined that the crystal corresponded to Pd(*N*,*N*-dimethyl β-alaninate)$_2$ (Figure 1). Subsequently we were pleased to find that crystalline Pd(*N*,*N*-dimethyl β-alaninate)$_2$ could be readily prepared in large quantities as an air-stable and moisture-stable palladium salt.

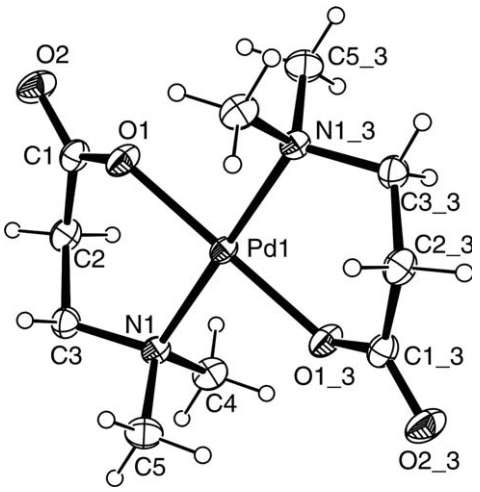


Figure 1 Crystal structure of Pd(*N*,*N*-dimethyl β-alaninate)$_2$

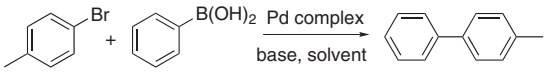
SYNTHESIS 2007, No. 3, pp 0393–0399
Advanced online publication: 12.01.2007
DOI: 10.1055/s-2007-965883; Art ID: F13106SS

With Pd(*N*,*N*-dimethyl β-alaninate)$_2$ in hand, we next examined whether this well-defined salt could be used directly, without any other additive, to catalyze the Suzuki reactions. To begin our study, we performed the Suzuki reaction between 4-bromotoluene and phenylboronic acid with 0.1 mol% of Pd(*N*,*N*-dimethyl β-alaninate)$_2$ using DMF as the solvent as previously described.[15] It was found that the reaction proceeded smoothly at 100 °C in a high yield without any inert gas protection (Table 1, entry 1). However, when the temperature was dropped to 50 °C, the yield decreased dramatically (entry 2). We then discovered that by adding water to the reaction we could obtain a high yield at 50 °C and even at room temperature (entries 3 and 4). By changing the base from K_2CO_3 to K_3PO_4 we further increased the yield from 89% to 98% (entries 5–7). An additional improvement was then made when the solvent was changed to EtOH–H_2O, which was more convenient to handle than DMF–H_2O. Using K_3PO_4 as the base in EtOH–H_2O, the Suzuki reaction could be complete within one hour at 50 °C with an excellent yield (99%), even when the catalyst loading was dropped to 0.01 mol% (entry 9).

Using the optimized reaction conditions (EtOH–H_2O/K_3PO_4, 50 °C, 1 h, in air), we next examined the application of Pd(*N*,*N*-dimethyl β-alaninate)$_2$ to the cross coupling of a variety of aryl halides with several arylboronic acids under 0.01 mol% catalyst loading (Table 2). The results indicated that Pd(*N*,*N*-dimethyl β-alaninate)$_2$ truly constituted an operationally simple, low-priced, yet highly efficient catalyst system for the Suzuki reaction of many aryl bromides. Both the electron-rich (deactivated) and electron-poor (activated) aryl bromides could be efficiently converted to the desirable products in high yields (entries 1–16). A highly sterically crowded substrate could also be tolerated (entry 17). The turnover numbers in most of the cases were about 10^4, demonstrating that Pd(*N*,*N*-dimethyl β-alaninate)$_2$ was a high-turnover-number catalyst. Besides aryl bromides, aryl iodides could also be successfully transformed to the desired Suzuki coupling products under the same conditions (entries 18–21). Nonetheless, Pd(*N*,*N*-dimethyl β-alaninate)$_2$ was not active enough to handle an aryl chloride (entries 22,23).

The above data demonstrated Pd(*N*,*N*-dimethyl β-alaninate)$_2$ to be a generally applicable, high-turnover-number catalyst for the Suzuki reaction. This strongly supported our previous proposition that *N*,*N*-dimethyl β-alanine was a catalytically active ligand in the combination of $Pd(OAc)_2$ and *N*,*N*-dimethyl β-alanine that could efficiently catalyze the Heck reaction.[15] At this point we noted an interesting yet puzzling behavior concerning these Pd-catalyzed reactions. That is, when the same Pd catalyst was utilized, the Suzuki reaction could be accomplished under much milder conditions than the Heck reaction. For our own Pd(*N*,*N*-dimethyl β-alaninate)$_2$ catalyst, the Heck reaction had to be performed at about 130 °C for over ten hours with 0.1 mol% of catalyst, whereas the Suzuki reaction could be carried out at 50 °C in an hour with only 0.01 mol% of catalyst (Scheme 1). Similar behavior has been reported in many other studies, where the Heck reaction was always achieved at a higher temperature, in a longer reaction time, and/or with a higher loading of the catalyst as compared to the Suzuki reaction.[16]

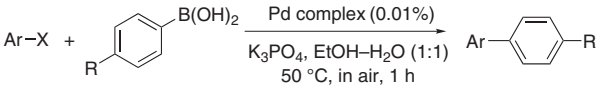
Table 1 Suzuki Reaction between 4-Bromotoluene and Phenylboronic Acid[a]

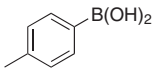
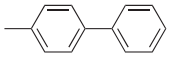
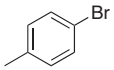
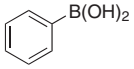
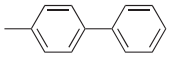
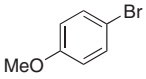
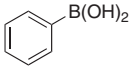
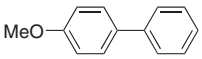
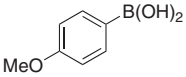
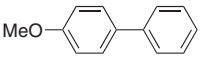
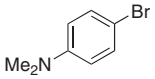
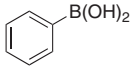
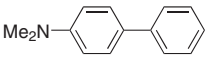
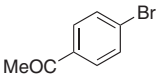
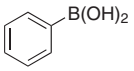
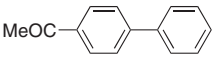
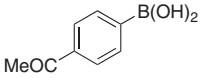
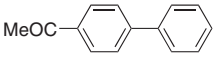
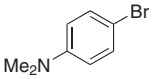
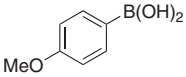
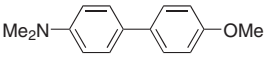
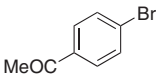
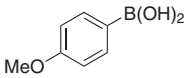
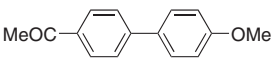
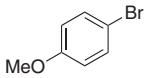
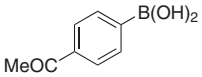
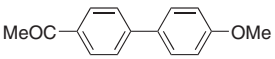
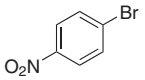
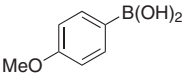
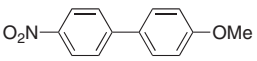
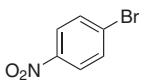
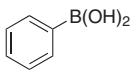
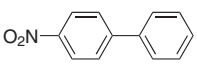
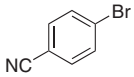
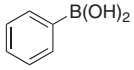
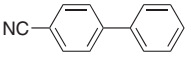


Entry	Catalyst (mol%)	Base	Temp (°C)	Time (h)	Solvent	Yield (%)[b]
1	0.1	K_2CO_3	100	13	DMF	96
2	0.1	K_2CO_3	50	10	DMF	10
3	0.1	K_2CO_3	50	3	DMF–H_2O[c]	89
4	0.1	K_2CO_3	r.t.	10	DMF–H_2O[c]	85
5	0.1	NaOAc	50	5	DMF–H_2O[c]	5
6	0.1	K_3PO_4	50	1	DMF–H_2O[c]	98
7	0.1	KF	50	3	DMF–H_2O[c]	96
8	0.1	K_2CO_3	50	1	EtOH–H_2O[d]	95
9	0.01	K_3PO_4	50	1	EtOH–H_2O[d]	99

[a] General conditions: 4-bromotoluene (5 mmol), phenylboronic acid (7.5 mmol), catalyst = Pd(*N*,*N*-dimethyl β-alaninate)$_2$, base (10 mmol), solvent (15 mL), in air.
[b] GC yields.
[c] DMF (7.5 mL) and H_2O (7.5 mL).
[d] EtOH (7.5 mL) and H_2O (7.5 mL).

Table 2 Suzuki Reactions Catalyzed by the Pd(*N*,*N*-Dimethyl β-alaninate)$_2$ Salt[a]



Entry	Aryl halide	Boronic acid	Product	Yield (%)[b]
1				98
2				99
3				96
4				98
5				97
6				98
7				96
8				91
9				99
10				96
11				98
12				97
13				99
14				97
15				88
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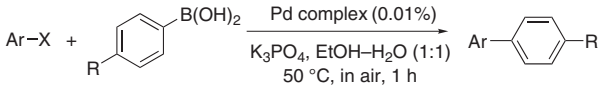
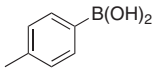
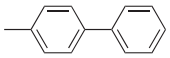
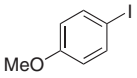
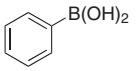
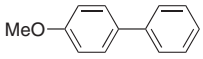
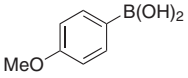
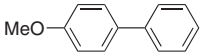
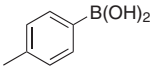
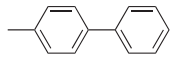
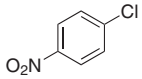
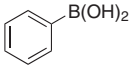
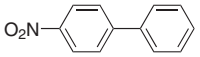
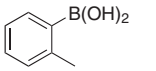
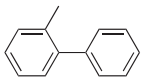
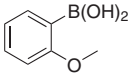
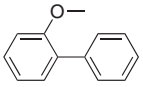
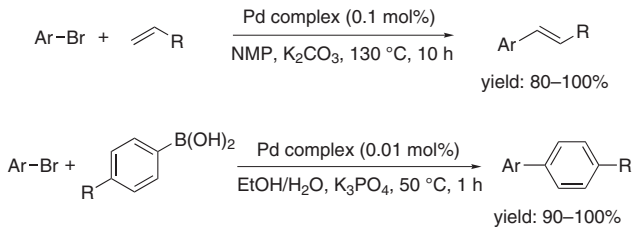
18				99

Table 2 Suzuki Reactions Catalyzed by the Pd(*N*,*N*-Dimethyl β-alaninate)$_2$ Salt[a] (continued)



Entry	Aryl halide	Boronic acid	Product	Yield (%)[b]
19				97
20				94
21				97
22				<20
23				<20
24				94
25				97

[a] Reaction conditions: aryl halide (5 mmol), arylboronic acid (7.5 mmol), Pd(*N*,*N*-dimethyl β-alaninate)$_2$ (0.0005 mmol), K_3PO_4 (10 mmol), EtOH (7.5 mL), H_2O (7.5 mL), in air.
[b] Isolated yield.

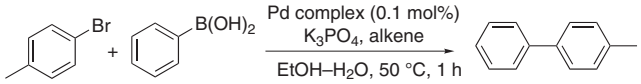


Scheme 1 Comparing the reactivity of Heck and Suzuki reactions. Pd complex = Pd(*N*,*N*-dimethyl β-alaninate)$_2$.

To further elucidate the different reactivity between the Heck and Suzuki reactions, we performed the following control experiments where a certain amount of alkene was added to the Suzuki reaction mixture of 4-bromotoluene and phenylboronic acid (Table 3). It was found that when 1 equivalent (or 100 mol%) of styrene was added to the Suzuki reaction mixture (Pd = 0.1 mol%), almost no 4-methylbiphenyl could be detected after one hour at 50 °C. Similarly, almost no 4-methylbiphenyl could be detected when 0.1 equivalent of styrene was added. After a further decrease of styrene to 0.01 equivalent (or 1 mol%), we started to observe the desired Suzuki reaction product (i.e. 4-methylbiphenyl) after one hour, albeit the yield was low (50%). Next we reduced the styrene loading to 10^{-3}, 10^{-4}, 10^{-5}, and 10^{-6} equivalents, where the corresponding yield of the desired 4-methylbiphenyl product increased dramatically from 65% to 96%. It is worth mentioning that we never observed any Heck-coupling product under any of the above reaction conditions.

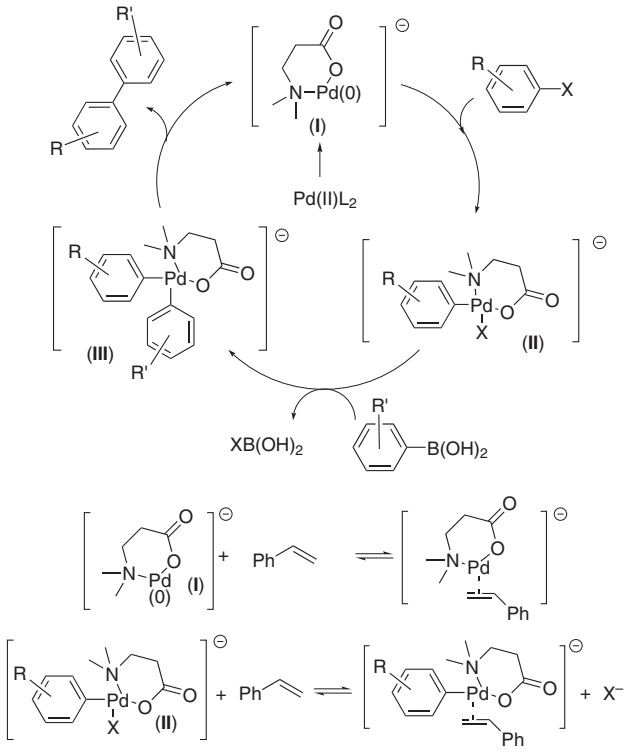
Using the above method we have also examined the effects of (*E*)-1,2-diphenylethene, triphenylethene, and 1,1,2,2-tetraphenylethene on the Suzuki reaction between 4-bromotoluene and phenylboronic acid. It was found again that the Suzuki reaction could not proceed well even when a sub-stoichiometric amount of olefin was present. To explain the observations, we propose the following mechanism (Scheme 2). First, a Pd(0) complex **I** with the ligand (*N*,*N*-dimethyl β-alanine) is generated from the reaction of Pd(II) with solvents or substrates.[17] Second, oxidative addition of aryl halide to **I** produces complex **II**, which undergoes transmetalation with the boronic acid to generate complex **III**. Finally, reductive elimination of **III** produces the desired coupling product and **I**. The reasons that addition of an olefin dramatically hampered the Suzuki reaction are two-fold: (1) both **I** and **II** could form complexes with the olefin that stops the catalytic cycle, and (2) only a small portion of Pd(II)L_2 is converted to the catalytically active Pd(0) complex **I** and therefore, a small amount of olefin is sufficient to slow down the turnover frequency. Thus, our experiments not only indicate that the Suzuki reaction was much more facile than the Heck reaction, but also demonstrate that the presence of an olefin can retard the Suzuki reaction.

Table 3 Suzuki Reaction in the Presence of Alkenes[a]



Added alkene (equiv)	 Yield (%) of 4-methylbiphenyl	 Yield (%) of 4-methylbiphenyl	 Yield (%) of 4-methylbiphenyl	 Yield (%) of 4-methylbiphenyl
1	0	0	–[b]	–[b]
0.1	0	20	27	–[b]
0.01	50	42	75	45
0.001	65	50	95	85
10^{-4}	74	74	98	90
10^{-5}	92	78	99	95
10^{-6}	96	92	99	98

[a] Reaction conditions: 4-bromotoluene (5 mmol), phenylboronic acid (7.5 mmol), Pd complex = Pd(*N*,*N*-dimethyl β-alaninate)$_2$, base (10 mmol), EtOH (7.5 mL), H_2O (7.5 mL), in air. GC yields.
[b] The alkene was not fully soluble under these conditions.



Scheme 2 Proposed mechanism for the Suzuki reaction catalyzed by Pd(*N*,*N*-dimethyl β-alaninate)$_2$

To summarize, in the present study we have synthesized a novel crystalline, air-stable, and moisture-stable Pd salt, Pd(*N*,*N*-dimethyl β-alaninate)$_2$. This salt was demonstrated to constitute a low-priced, phosphine-free, yet high-turnover-number catalyst for the Suzuki reactions of various aryl bromides and iodides under mild and simple reaction conditions. Furthermore, we observed that the presence of an olefin could dramatically hamper the Suzuki reaction. This finding may provide interesting mechanistic insights into the lower reactivity of the Heck reaction as compared to the Suzuki reaction.

All chemicals were purchased from Acros. NMR spectra were recorded on a Bruker AV300 spectrometer in $CDCl_3$ using TMS as internal standard.

Pd(*N*,*N*-Dimethyl β-Alaninate)$_2$

A mixture of *N*,*N*-dimethyl-β-alanine (2 equiv) and K_2PdCl_4 (1 equiv) was stirred in H_2O at r.t. for 10 min. The solution was adjusted to pH 8 with aq 10% NaOH whereupon a precipitate was formed. The yellow solid obtained was collected by filtration and dried under vacuum; yield: 72%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.45 (t, *J* = 5.25 Hz, 4 H), 2.56 (m, 4 H), 2.57 (s, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.5, 49.0, 60.1, 176.0.

Suzuki Reaction; General Procedure

To a mixture of aryl halide (5 mmol), arylboronic acid (7.5 mmol), Pd(*N*,*N*-dimethyl β-alaninate)$_2$ (0.0005 mmol), and K_3PO_4 (10 mmol) were added H_2O (7.5 mL) and EtOH (7.5 mL). The mixture was stirred at 50 °C in air for 1 h. The resulting mixture was cooled to r.t. and extracted with Et_2O. The Et_2O layer was separated, dried, and concentrated. The residue was purified by chromatography (hexane–EtOAc) to afford the desired product (Table 2).

4-Methylbiphenyl[18]

^{1}H NMR: δ = 2.38 (s, 3 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 7.32 (m, 1 H), 7.41 (t, *J* = 7.5 Hz, 2 H), 7.48 (d, *J* = 8.1 Hz, 2 H), 7.56 (d, *J* = 7.5 Hz, 2 H).

^{13}C NMR: δ = 21.22, 127.13, 128.84, 129.61, 137.14, 138.52, 141.32.

4-Methoxybiphenyl[19]
^{1}H NMR: δ = 3.84 (s, 3 H), 6.97 (m, 2 H), 7.30 (d, *J* = 7.2 Hz,1 H), 7.40 (t, *J* = 7.5 Hz, 2 H), 7.53 (m, 4 H).

^{13}C NMR: δ = 55.48, 114.39, 126.82, 126.90, 128.31, 128.88, 133.95, 141.00, 159.35.

4-Dimethylaminobiphenyl[6]
^{1}H NMR: δ = 3.00 (s, 3 H), 6.83 (s, 2 H), 7.30 (d, *J* = 7.2 Hz, 1 H), 7.40 (t, *J* = 7.5 Hz, 2 H), 7.53 (m, 4 H).

^{13}C NMR: δ = 40.56, 112.87, 126.05, 126.32, 127.74, 128.74, 129.26, 141.29, 150.02.

4-Acetylbiphenyl[20]
^{1}H NMR: δ = 2.64 (s, 3 H), 7.42 (m, 1 H), 7.47 (m, 2 H), 7.63 (m, 2 H), 7.68 (m, 2 H), 8.03 (m, 2 H).

^{13}C NMR: δ = 26.66, 127.24, 127.30, 128.29, 128.96, 129.01, 135.93, 139.90, 145.78, 197.70.

4-Methoxy-4′-dimethylaminobiphenyl[21]
^{1}H NMR: δ = 2.99 (s, 6 H), 3.83 (s, 3 H), 6.83 (m, 2 H), 6.94 (d, *J* = 8.7 Hz, 2 H), 7.46 (m, 4 H).

^{13}C NMR: δ = 40.81, 55.45, 113.12, 114.27, 127.44, 129.38, 134.10, 149.73, 158.43.

4-Acetylamino-4′-methoxybiphenyl[22]
^{1}H NMR: δ = 2.62 (s, 3 H), 3.86 (s, 3 H), 7.00 (d, *J* = 8.7 Hz, 2 H), 7.57 (d, *J* = 8.7 Hz, 2 H), 7.64 (d, *J* = 8.5 Hz, 2 H), 8.00 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR: δ = 26.67, 55.47, 114.53, 126.69, 128.45, 129.04, 132.34, 135.42, 145.45, 160.05, 197.75.

4-Methoxy-4′-nitrobiphenyl[22]
^{1}H NMR: δ = 3.87 (s, 3 H), 7.01 (d, *J* = 8.7 Hz, 2 H), 7.58 (d, *J* = 8.7 Hz, 2 H), 7.68 (d, *J* = 8.7 Hz, 2 H), 8.26 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR: δ = 55.55, 114.76, 124.25, 127.18, 128.68, 131.20, 146.70, 147.33, 160.61.

4-Nitrobiphenyl[23]
^{1}H NMR: δ = 7.44–7.52 (m, 3 H), 7.61 (m, 2 H), 7.73 (d, *J* = 8.9 Hz, 2 H), 8.29 (d, *J* = 8.9 Hz, 2 H).

^{13}C NMR: δ = 124.14, 127.43, 127.83, 129.00, 129.22, 138.80, 147.65.

4-Cyanobiphenyl[9]
^{1}H NMR: δ = 7.44–7.48 (m, 3 H), 7.60 (m, 2 H), 7.67–7.75 (m, 4 H).

^{13}C NMR: δ = 110.89, 118.99, 127.24, 127.73, 128.71, 129.15, 132.61, 139.14, 145.64.

4-Cyano-4′-methoxybiphenyl[22]
^{1}H NMR: δ = 3.86 (s, 3 H), 7.01 (d, *J* = 8.7 Hz, 2 H), 7.53 (d, *J* = 8.6 Hz, 2 H), 7.63 (d, *J* = 8.2 Hz, 2 H), 7.69 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR: δ = 55.34, 109.97, 114.51, 119.09, 127.00, 128.30, 131.33, 132.50, 145.08, 160.18.

4-Hydroxybiphenyl[7]
^{1}H NMR: δ = 4.81 (s, 1 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 7.26 (m, 1 H), 7.44 (m, 2 H), 7.50 (d, *J* = 8.6 Hz, 2 H), 7.55 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR: δ = 115.79, 126.87, 128.54, 128.88, 134.17, 140.90, 155.20.

***p*-Terphenyl**[18]
^{1}H NMR: δ = 7.34 (m, 2 H), 7.46 (m, 4 H), 7.63–7.67 (m, 8 H).

^{13}C NMR: δ = 127.19, 127.49, 127.65, 128.96, 140.26, 140.84.

2,6-Dimethylbiphenyl[24]
^{1}H NMR: δ = 2.03 (s, 6 H), 7.08–7.16 (m, 5 H), 7.34 (m, 1 H), 7.35–7.44 (m, 2 H).

^{13}C NMR: δ = 20.98, 126.73, 127.15, 127.41, 128.54, 129.16, 136.18, 141.23, 142.00.

2-Methylbiphenyl[25]
^{1}H NMR: δ = 2.27 (s, 3 H), 7.23–7.26 (m, 4 H), 7.30–7.35 (m, 3 H), 7.38–7.41 (m, 2 H).

^{13}C NMR: δ = 20.58, 125.89, 126.88, 127.37, 128.19, 129.32, 129.92, 130.43, 135.44, 142.08, 142.12.

2-Methoxybiphenyl[25]
^{1}H NMR: δ = 3.80 (s, 3 H), 7.97–7.02 (m, 2 H), 7.29–7.34 (m, 3 H), 7.40 (m, 2 H), 7.52 (d, *J* = 6.9 Hz, 2 H).

^{13}C NMR: δ = 55.58, 111.35, 120.93, 126.98, 128.06, 128.70, 129.68, 130.83, 130.97, 138.66, 156.56.

Acknowledgment

We thank NSFC (No. 20332020 and 20472079) for financial support.

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(3) Practically speaking, any catalyst displaying a turnover number (TON) of greater than 10^3, i.e. a catalyst that can lead to complete conversion of starting materials at a load of 0.1% mol, will be considered as a high-turnover-number catalyst.

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