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Pd(quinoline-8-carboxylate)$_2$ as a Low-Priced, Phosphine-Free Catalyst for Heck and Suzuki Reactions

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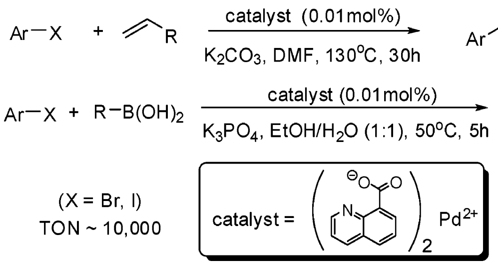
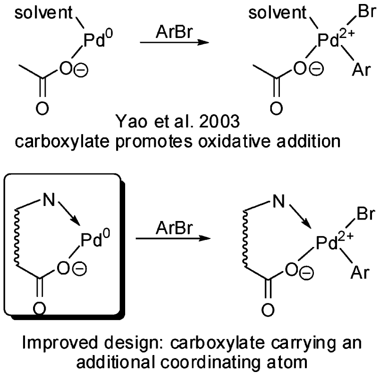


N,*O*-Bidentate compounds were systematically evaluated as phosphine-free ligands for Pd-catalyzed C−C bond-formation reactions through kinetic measurements. Pd(quinoline-8-carboxylate)$_2$ was identified as one of the most efficient, yet still low-priced, phosphine-free catalysts for Heck as well as Suzuki reactions of unactivated aryl bromides with high turnover numbers up to ca. 10,000.

Pd-catalyzed C−C bond-formation reactions such as the Heck and Suzuki cross couplings are playing important roles in modern organic synthesis.[1] These cross-coupling reactions are usually performed with 1−5 mol % of Pd catalyst along with phosphine ligands, which sometimes creates practical problems because organophosphines tend to be expensive, poisonous, and air sensitive.[2] Accordingly, an interesting current challenge is to develop Pd catalysts that can utilize inexpensive phosphine-free ligands. In this regard a number of ligands including *N*-heterocyclic carbenes (NHC),[3] oxazolines,[4] amines,[5] Schiff bases,[6] pyridines,[7] hydrazones,[8] guanidines,[9] pyrazoles,[10] tetrazoles,[11] quinolines,[12] carbazones,[13] imidazoles,[14] thioureas,[15] and 1,3-dicarbonyl compounds[16] have been examined for Pd catalysis recently. Note that not all of these phosphine-free ligands (e.g., NHC) are less expensive than phosphines. On the other hand, Yao et al. reported in 2003[17] that Pd(OAc)$_2$, albeit being very simple, could also efficiently catalyze the Heck reaction where the acetate anion was proposed to function as ligand. This interesting finding was consistent with the theory of Amatore and Jutand[18] who claimed that coordination by anionic carboxylates could enhance the activity of Pd toward oxidative addition.

Prompted by Yao's pioneering discovery, we hypothesized that it was possible to design phosphine-free Pd catalysts more efficient, yet still low-priced, than Pd(OAc)$_2$ by strategically incorporating an additional coordinating site into the acetate anion (Scheme 1). This hypothesis was partly validated by our recent study on the use of amino acids as ligands for Pd-catalyzed Heck reactions[19] and an earlier related study by Reetz

SCHEME 1. Improved Design of Phosphine-Free Ligands for Pd Catalysis by Incorporating an Additional Coordinating Atom



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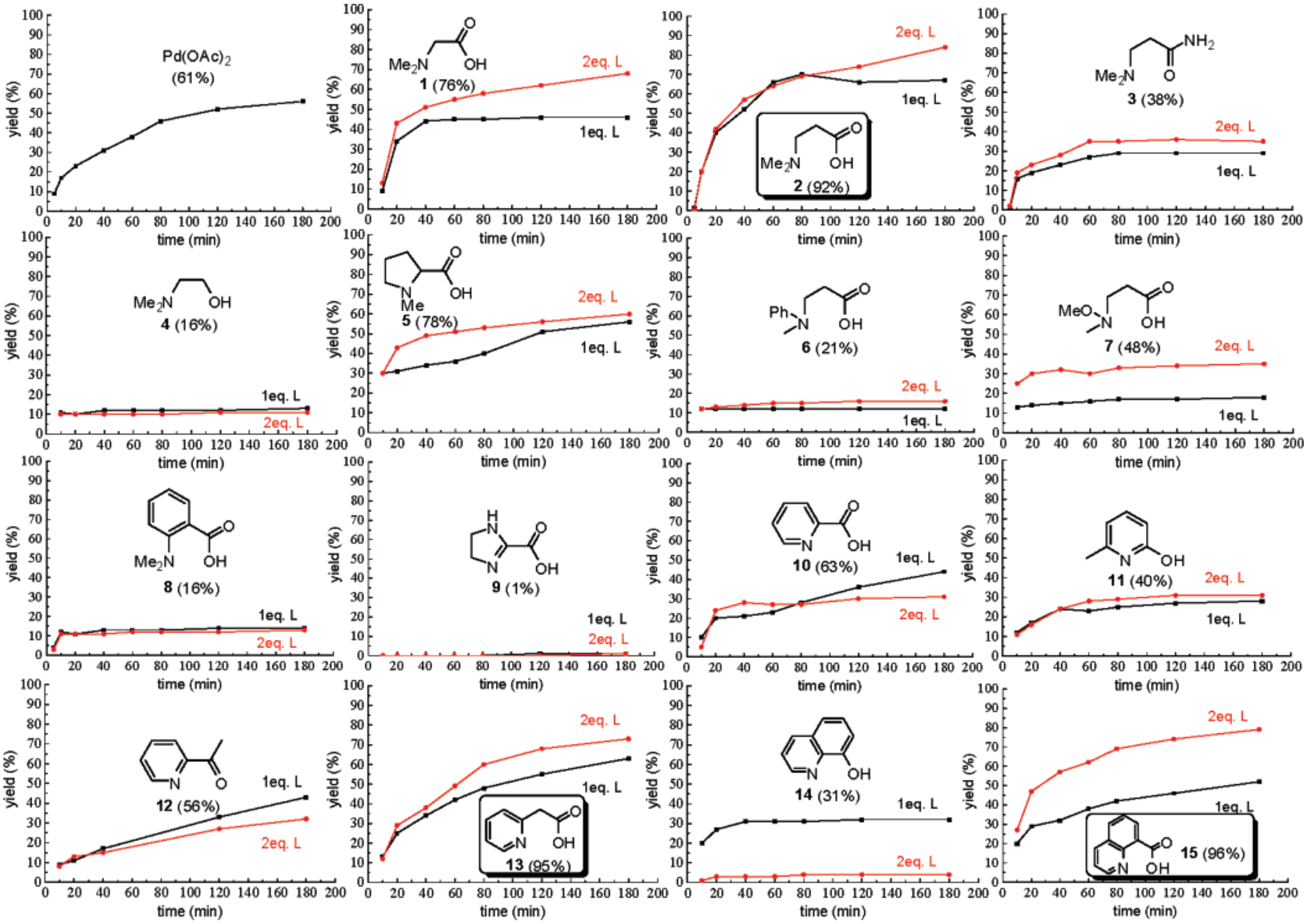

FIGURE 1. Initial velocity of the Heck reaction between PhBr and styrene. Conditions: PhBr (5 mmol), styrene (7.5 mmol), K_2CO_3 (10 mmol), DMF (5 mL), $Pd(OAc)_2 = 0.005$ mol, $Pd(OAc)_2$:ligand = 1:1 or 1:2, temperature = 130 °C, under Ar. The values in parentheses are the GC yields measured after each reaction is stirred for 12 h.

et al.[20] Here we further extended our search for more efficient phosphine-free ligands for Pd catalysis by systematically evaluating various *N*,*O*-bidentate compounds. Through detailed kinetic measurements we demonstrated the significant effect of incorporating an additional coordinating site into the acetate. We also found that Pd(quinoline-8-carboxylate)$_2$ constituted one of the most efficient, yet low-priced, phosphine-free catalysts for the Heck and Suzuki reactions with fairly high turnover numbers up to ca. 10,000 for unactivated aryl bromides.

In designing our experiments we fixed the solvent as DMF.[21] By using $Pd(OAc)_2$ in combination with 1 or 2 equiv of an *N*,*O*-bidentate ligand, we monitored the progress of the Heck reaction between phenyl bromide and styrene by measuring the GC yields at different intervals after the reaction was initiated (Figure 1). It was found that in the absence of any other ligand, $Pd(OAc)_2$ indeed could catalyze the Heck reaction, but the maximum yield was 61% (compared to 74% as reported by Yao et al.[17] under similar conditions). Adding ligand **1** increased the yield to 76%, whereas adding ligand **2** further increased the yield to 92%. Evidently the attachment of an amino group to acetate could produce a significant effect on the catalysis.

As aforementioned,[18] coordination to Pd by anionic carboxylates could facilitate oxidative addition. In agreement with this theory, our experiments showed that adding **3** or **4** dramatically decreased the yields where the carboxylate oxygen was replaced by an amide or alcohol oxygen. Furthermore, it was found that the nature of the nitrogen atom also had a strong effect on the catalysis. Thus, ligand **5** gave a yield of 78% that was comparable to that of ligand **1**. Ligands **6**−**9** gave yields that were much lower than the yield provided by $Pd(OAc)_2$. Ligand **10**, on the other hand, gave a yield (63%) that was slightly better than that of $Pd(OAc)_2$. These data indicated that alkylamine and pyridine were good neighboring groups to enhance the effect of a carboxylate group, whereas arylamine, methoxyamine, and amidine were not.

Given the fact that **2** was better than **1**, we next added a methylene group into **10**, ending up with ligand **13**. It was found that **13** gave a GC yield of 95% that was higher than the yield provided by ligand **2**. Encouraged by this finding, we then incorporated a phenyl ring into **13** and obtained ligand **15**. To our delight, this particular ligand was found to give the highest GC yield (i.e., 96%) among all the *N*,*O*-bidentate ligands that we had examined. Noteworthy control experiments with ligands

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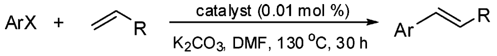
(21) DMA was used in Yao's study (ref 17), but DMF is more user-friendly than DMA in terms of solvent removal.

TABLE 1. Heck-Type Reactions Catalyzed by Pd(quinoline-8-carboxylate)$_2$[a]



entry	ArX	R	yield[b] (%)	entry	ArX	R	yield[b] (%)
1	PhBr	Ph	94	15	4-NC−C_6H_4Br	Ph	87
2	PhBr	CO_2Bu^n	91	16	4-NC−C_6H_4Br	CO_2Bu^n	71
3	4-O_2N−C_6H_4Br	Ph	97	17	4-Ph−C_6H_4Br	Ph	71
4	4-O_2N−C_6H_4Br	CO_2Bu^n	35	18	4-Ph−C_6H_4Br	CO_2Bu^n	74
5	4-Me−C_6H_4Br	Ph	91	19	3-F_3C-C_6H_4Br	Ph	98
6	4-Me−C_6H_4Br	CO_2Bu^n	88	20	3-F_3C-C_6H_4Br	CO_2Bu^n	92
7	4-MeO−C_6H_4Br	Ph	78	21	3-bromopyridine	Ph	96
8	4-MeO−C_6H_4Br	CO_2Bu^n	73	22	3-bromopyridine	CO_2Bu^n	98
9	4-OHC−C_6H_4Br	Ph	93	23	PhI	Ph	92
10	4-OHC−C_6H_4Br	CO_2Bu^n	82	24	PhI	CO_2Bu^n	87
11	4-MeOC−C_6H_4Br	Ph	92	25	4-MeO−C_6H_4I	Ph	73
12	4-MeOC−C_6H_4Br	CO_2Bu^n	39	26	PhCl	Ph	0
13	3-NC−C_6H_4Br	Ph	90	27	4-NO_2-C_6H_4Cl	Ph	35
14	3-NC−C_6H_4Br	CO_2Bu^n	92				

[a] Reaction conditions: Aryl halide (5 mmol), olefin (7.5 mmol), K_2CO_3 (10 mmol), DMF (10 mL), catalyst = **18**, under Ar. [b] Isolated yield.

11, **12**, and **14** demonstrated that the presence of a carboxylate group was crucial for the catalysis efficiency.

The optimal ligand:Pd ratio was found to be 2:1 for ligands **2**, **13**, and **15**. As a result we synthesized the Pd(II) salts of **2**, **13**, and **15** by mixing 2 equiv of sodium *N*,*N*-dimethyl β-alanate, 2-pyridylacetate, or quinoline-8-carboxylate with 1 equiv of K_2PdCl_4 in water, which provided the target Pd complexes **16**, **17**, and **18** as solid precipitates. Using the pure Pd salts as catalyst we next lowered the Pd loading to 0.01 mol % in the cross coupling between phenyl bromide and styrene. It was found that the maximum turnover numbers for catalysts **16**, **17**, and **18** were 1600, 3800, and 9400, respectively (Figure 2). The turnover number of catalyst **18** is about one magnitude lower than the best phosphine-free Pd catalysts currently available (e.g., Pd pincers and Pd NHC complexes).[22] Nonetheless, the turnover number of **18** (ca. 10^4) is sufficiently high from practical considerations.

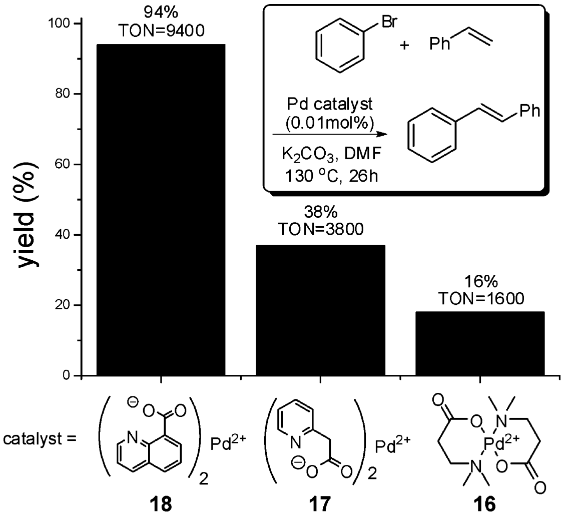


FIGURE 2. Maximum turnover numbers given by the best three *N*,*O*-bidentate ligands.

To explore the scope of the reactions catalyzed by **18**, we next examined the application of **18** to the cross coupling of a variety of aryl halides with styrene and *n*-butyl acrylate under 0.01 mol % catalyst loading (See Table 1). The results indicated that **18** constituted a simple, yet efficient, phosphine-free catalyst for many Heck-type reactions of aryl bromides. Both the electron-rich (deactivated) and electron-poor (activated) aryl bromides could be efficiently converted to the desirable products in high yields. The turnover numbers in most of the cases were about 10^4. Besides aryl bromides, aryl iodides could also be successfully used under the same reaction conditions (entries 23−25). Nonetheless, **18** was not active enough to handle an aryl chloride unless it was activated by electron-withdrawing substituents (such as 4-NO_2).

TABLE 2. Suzuki Reactions Catalyzed by Pd(quinoline-8-carboxylate)$_2$[a]

$$\mathrm{ArX} + \mathrm{R{-}B(OH)_2} \xrightarrow[\mathrm{K_3PO_4,\ EtOH/H_2O,\ 50\ ^\circ C,\ 5\ h}]{\text{catalyst (0.01 mol\%)}} \mathrm{Ar{-}R}$$

entry	ArX	R	yield[b] (%)
1	PhBr	4-Me−C_6H_4-	96
2	4-Me−C_6H_4Br	Ph-	98
3	4-MeO−C_6H_4Br	Ph-	93
4	PhBr	4-MeO−C_6H_4-	95
5	4-MeCO−C_6H_4Br	Ph-	95
6	4-MeCO−C_6H_4Br	4-MeO−C_6H_4-	93
7	4-O_2N−C_6H_4Br	4-MeO−C_6H_4-	89
8	4-O_2N−C_6H_4Br	Ph-	91
9	4-NC−C_6H_4Br	Ph-	96
10	4-MeCO−C_6H_4I	Ph-	99
11	PhI	4-Me−C_6H_4-	97
12	4-MeO−C_6H_4I	Ph-	88
13	PhI	4-MeO−C_6H_4-	94
14	4-Me−PhCl	Ph-	0
15	4-O_2N−C_6H_4Cl	Ph-	Trace

[a] Conditions: aryl halide (5 mmol), boronic acid (7.5 mmol), K_3PO_4 (10 mmol), EtOH/H_2O (7.5/7.5 mL), catalyst = **18**, in air. [b] Isolated yield.

Having found that **18** was an excellent catalyst for the Heck reactions, we next examined whether **18** could also facilitate the Suzuki reactions. To our satisfaction, it was found that **18** was active enough to promote the Suzuki reactions under relatively mild conditions in air and in the presence of water

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(Table 2). Both electron-rich and electron-poor aryl bromides could be successfully converted to the desirable products very rapidly (ca. 5 h). The turnover numbers were as high as ca. 10^4. Furthermore, aryl iodides were excellent substrates for the reaction (entries 10−13), although aryl chlorides could not be converted effectively (entries 14−15). It is worth noting that phosphine-free Suzuki reactions were achieved previously either by using expensive Pd pincers and Pd NHC complexes,[23] or by using low-priced ligands but with a relatively high load of Pd (i.e., >1 mol %).[24] In comparison, the new phosphine-free catalyst (i.e., **18**) described here is advantageous from the economic point of view.

To summarize, in the present study we systematically tested the hypothesis that incorporating an additional coordination site to the acetate anion would provide more efficient yet low-priced ligands for Pd catalyzed C−C bond-formation reactions than $Pd(OAc)_2$. It was found that alkylamine and pyridine were good neighboring groups to enhance the effect of a carboxylate group in Pd catalysis, whereas arylamine, methoxyamine, and amidine were not. The best *N*,*O*-bidentate ligand turned out to be quinoline-8-carboxylate, and $Pd(quinoline\text{-}8\text{-}carboxylate)_2$ constituted an ideal Pd catalyst[25] that was structurally simple, synthetically inexpensive, and chemically stable. Synthetic examinations demonstrated that $Pd(quinoline\text{-}8\text{-}carboxylate)_2$ could smoothly catalyze the Heck and Suzuki reactions of unactivated aryl bromides and iodides with fairly high turnover numbers up to ca. 10^4.

Experimental

Synthesis of $Pd(quinoline\text{-}8\text{-}carboxylate)_2$. A mixture of 2 equiv of sodium quinoline-8-carboxylate and 1 equiv of K_2PdCl_4 was stirred in water at room temperature for 10 min. The precipitate was filtered and dried under vacuum to afford a yellow solid which could not dissolve in the common organic solvents (69%). Elemental analysis calcd for $C_{20}H_{12}N_2O_4Pd$: C 53.33; H 2.67; N 6.22 (O 14.22, Pd 23.56). Found: C 52.93; H 2.67; N 6.16.

Typical Experimental Procedure for the Heck Reaction. A mixture of phenyl bromide (5 mmol), styrene (7.5 mmol), **18** (0.5×10^{-3} mmol), and K_2CO_3 (10 mmol) in 10 mL of dry DMF was stirred under Ar at 130 °C for the desired time. The mixture was washed by water and extracted by ether, and then the solvent was evaporated. The residue was purified by flash column chromatography to afford the desired product. **(*E*)-1,2-Diphenylethene:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (s, 2H), 7.24−7.28 (m, 2H), 7.35 (t, 4H, $J = 7.5$ Hz), 7.52 (d, 4H, $J = 7.7$ Hz).[26]

Typical Experimental Procedure for the Suzuki Reaction. A mixture of *p*-methylphenyl bromide (5 mmol), phenyl boronic acid (7.5mmol), **18** (0.5×10^{-3} mmol), and K_3PO_4 (10 mmol) in methanol/H_2O (7.5 mL/7.5 mL) was stirred at 50 °C for the desired time. The mixture was washed by water and extracted by ether, and then the solvent was evaporated. The residue was purified by flash column chromatography to afford the desired product. **4-Methylbiphenyl:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 7.25 (d, 2H, $J = 8.0$ Hz), 7.33 (m, 1H), 7.42 (t, 2H, $J = 7.6$ Hz); 7.49 (d, 2H, $J = 8.2$ Hz), 7.57 (m, 2H).[27]

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Supporting Information Available: Experimental procedures, analytical data, and scanned spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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[23] A very recent example: Navarro, O.; Marion, N.; Mei, J.; Nolan, S. P. *Chem. Eur. J.* **2006**, *12*, 5142.

[24] Some examples: (a) Zhang, G. *Synthesis* **2005**, 537. (b) Najera, C.; Gil-Molto, J.; Karlstrom, S. *Adv. Synth. Catal.* **2004**, *346*, 1798.

[25] Strictly speaking, $Pd(quinoline\text{-}8\text{-}carboxylate)_2$ was a precatalyst because Pd(II) must be reduced to Pd(0) to catalyze the Heck and Suzuki reactions. For a mechanistic study, see: Cardenas, D. J.; Martin-Matute, B.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 5033.

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