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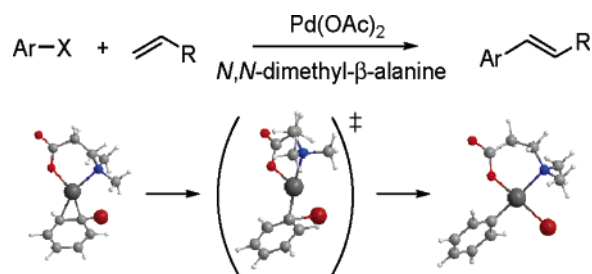
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ABSTRACT



N,N-Dimethyl- β -alanine was found to be a more powerful phosphine-free ligand than the previously reported ligand, *N,N*-dimethylglycine, in the Pd-catalyzed Heck reaction for a variety of aryl bromides, aryl iodides, and activated aryl chlorides with a practical turnover number of 10^3 . Both kinetic and theoretical studies suggested that *N,N*-dimethyl- β -alanine led to faster oxidative addition of an aryl halide to Pd than *N,N*-dimethylglycine.

The Pd-catalyzed cross-coupling of olefins with aryl halides is known as the Heck reaction.¹ This reaction, normally performed with 1–5% mol of Pd catalyst along with phosphine ligands, has become a widely used C–C bond-forming process in academic institutions. However, industrial applications of the Heck reaction are still rare, 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, many phosphine ligands are even more expensive, and they are not pleasant to work with as they are poisonous, air sensitive, and subject to P–C bond degradation at elevated temperature. Accordingly, one of the current focuses in the field is the development of high-turnover-number catalysts (HTC)³ that utilize inexpensive, preferentially nonphosphine, ligands.

To date, a number of phosphine-free catalysts have been examined for the Heck reaction. Among them, the pallada-

cycle catalysts have been shown to have great performance.⁴ However, increasing evidence points to the view that palladacycles are catalytically inactive and they simply function as sources of Pd(0) (i.e., pre-catalysts).² Another interesting class of ligands is heterocyclic carbene.⁵ Both mono- and bis-carbenes have been shown to give high turnover numbers (TONs) in the Heck reaction, but it is often puzzling to see that their catalytic performances are constant regardless of the ligation state of the catalyst.² Thus, more kinetic and mechanistic work is needed in order to understand how carbene ligands operate in Pd catalysis. In addition, alternative catalytic systems represent the N-, O-, and S-centered ancillary ligand complexes of Pd. Although less

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(3) Practically speaking, any catalyst displaying $>10^3$ turnover number, i.e., a catalyst that can lead to complete conversion of starting materials at a load of 0.1% mol, will be considered as an HTC.

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explored, this type of ligands has been shown lately to have interesting applications in the Heck reaction. Very recent examples include thioureas,⁶ imines and oximes,⁷ bispyridines,⁸ phenanthrolines,⁹ hydrazones,¹⁰ tetramethylguanidines,¹¹ hydroxyquinolines,¹² oxazolines,¹³ thiosemicarbazones,¹⁴ tetrazoles,¹⁵ bisimidazoles,¹⁶ and amino acids.¹⁷ These phosphine-free ligands are potentially advantageous for being chemically stable and economically inexpensive. As a result, further synthetic as well as mechanistic studies on these ligands are highly warranted.

We recently started a systematic study on how to use more economically competitive metals (e.g., Fe, Ni, and Cu) and/or ligands (in particular, phosphine-free ligands) to accomplish the classical Pd-catalyzed reactions.¹⁸ We aim at not only finding novel catalysts but also, more importantly, a mechanistic understanding of the catalytic processes. In continuing such efforts, our attention was drawn to an intriguing finding by Reetz et al. that Pd(II) salts in the presence of *N,N*-dimethylglycine ligand (**1**) constitute “the simplest and one of the most reactive and selective catalyst systems for the Heck reaction”.¹⁷ Herein, we report our finding that *N,N*-dimethyl- β -alanine (**2**) is an even more efficient ligand for the Heck reaction (Figure 1). Furthermore,

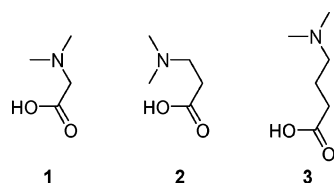


Figure 1. N,O-Bidentate ligands used for the Heck reaction.

we report the first theoretical study on how the *N,O*-bidentate ligands operate in the Pd catalysis.

To begin our study, we noted that the optimal reaction condition reported by Reetz et al. consisted of 1.5% mol of

Pd and 30% mol of **1**. Reaction at 130 °C for 10 h provided the desired product in an almost quantitative yield. It is worth noting that **1** would create a five-membered ring with Pd when they form a bidentate complex. We wondered whether by changing the ring size we could attain a more efficient catalyst. Thus, we studied the use of **2** in the Heck reaction between bromobenzene and styrene and compared its performance with **1** and 4-(*N,N*-dimethylamino)butanoic acid (**3**).¹⁹ In our study, the ratio between Pd and the ligand was set to 1:1, contrary to 1:20 in Reetz's study. After a few solvent systems were examined, we concluded that NMP was the best solvent (see Table 1). Instead of 1 mol mol, it was

Table 1. Heck Reaction between Bromobenzene and Styrene^a

entry	Pd (mol %)	ligand	base	T (°C)	time (h)	solvent	yield ^b (%)
1	1	2	K ₂ CO ₃	130	10	DMF	86
2	1	2	K ₂ CO ₃	130	10	DMA	83
3	1	2	K ₂ CO ₃	130	10	DMSO	38
4	1	2	K ₂ CO ₃	130	10	NMP	99
5	0.1	2	K ₂ CO ₃	130	10	NMP	99
6	0.01	2	K ₂ CO ₃	130	20	NMP	96
7	0.1		K ₂ CO ₃	130	10	NMP	42
8	0.1	1	K ₂ CO ₃	130	10	NMP	81
9	0.1	3	K ₂ CO ₃	130	10	NMP	70

^a Reaction conditions: bromobenzene (0.5 mmol), styrene (0.75 mmol), base (1 mmol), solvent (1 mL), under Ar. ^b GC yields.

found that 0.1 mol % of Pd/**2** was active enough for giving a quantitative yield in 10 h. A further decrease of Pd/**2** to 0.01 mol % could lead to a significant TON as high as about 10⁴. However, the relatively long reaction time would not be considered desirable for pragmatic applications.² Compared to Pd/**2**, the yield in the absence of any ligand was much lower (42%) presumably due to the rapid formation of Pd black, a visible phenomenon we confirmed in our experiment. Furthermore, the yields for Pd/**1** (81%) and Pd/**3** (70%) were also determined to be lower than that of Pd/**2** (99%) under the same reaction conditions. Thus, we concluded temporarily that **2** was superior to **1** and **3** in the catalysis.

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(19) Compound **1** was purchased. Compound **2** was prepared by methylation of β -alanine. Compound **3** was prepared by hydrolysis and subsequent methylation of *N*-methyl-2-pyrrolidone. They were all used as their hydrochloride salts.

Using the optimized reaction conditions, we next examined the application of ligand **2** to the cross coupling of a variety of aryl halides with styrene and *tert*-butyl acrylate under 0.1 mol % catalyst loading (See Table 2). The results indicated

Table 2. Heck-Type Reactions Facilitated by Ligand **2**^a

$$\text{ArX} + \text{CH}_2=\text{CH-R} \xrightarrow[\text{NMP, 130 } ^\circ\text{C, 10 h}]{\text{Pd(OAc)}_2 \text{ (0.1 mol \%), } \mathbf{2} \text{ (0.1 mol \%), K}_2\text{CO}_3} \text{Ar-CH=CH-R}$$

entry	ArX	R	yield ^b (%)
1	PhBr	Ph	98
2	PhBr	CO ₂ Bu ⁿ	98
3 ^c	4-O ₂ NC ₆ H ₄ Br	Ph	90
4 ^c	4-O ₂ NC ₆ H ₄ Br	CO ₂ Bu ⁿ	53
5	4-MeC ₆ H ₄ Br	Ph	97
6	4-MeC ₆ H ₄ Br	CO ₂ Bu ⁿ	98
7	1-C ₁₀ H ₇ Br	CO ₂ Bu ⁿ	95
8	4-MeOC ₆ H ₄ Br	Ph	96
9	4-MeOC ₆ H ₄ Br	CO ₂ Bu ⁿ	94
10	4-HOCC ₆ H ₄ Br	Ph	98
11	4-OHCC ₆ H ₄ Br	Ph	86
12	4-OHCC ₆ H ₄ Br	CO ₂ Bu ⁿ	92
13	4-MeOCC ₆ H ₄ Br	Ph	98
14	4-MeOCC ₆ H ₄ Br	CO ₂ Bu ⁿ	69
15	4-HOC ₆ H ₄ Br	Ph	74
16	4-HOC ₆ H ₄ Br	CO ₂ Bu ⁿ	80
17	3-NCC ₆ H ₄ Br	Ph	94
18	3-NCC ₆ H ₄ Br	CO ₂ Bu ⁿ	90
19	4-NCC ₆ H ₄ Br	Ph	98
20	4-NCC ₆ H ₄ Br	CO ₂ Bu ⁿ	70
21	4-PhC ₆ H ₄ Br	Ph	50
22	4-PhC ₆ H ₄ Br	CO ₂ Bu ⁿ	75
23	3-F ₃ CC ₆ H ₄ Br	Ph	98
24	3-F ₃ CC ₆ H ₄ Br	CO ₂ Bu ⁿ	92
25	2-bromopyridine	Ph	nr ^e
26	2-bromopyridine	CO ₂ Bu ⁿ	<20 ^f
27	3-bromopyridine	Ph	98
28	3-bromopyridine	CO ₂ Bu ⁿ	99
29 ^d	4-BrC ₆ H ₄ Br	CO ₂ Bu ⁿ	88
30	PhI	Ph	97
31	PhI	CO ₂ Bu ⁿ	98
32	4-MeOC ₆ H ₄ I	Ph	88
33	4-MeOC ₆ H ₄ I	CO ₂ Bu ⁿ	96
34	4-MeOCC ₆ H ₄ I	Ph	90
35	4-MeOCC ₆ H ₄ I	CO ₂ Bu ⁿ	53
36	PhCl	Ph	nr ^e
37	4-MeOCC ₆ H ₄ Cl	Ph	96
38	4-MeOCC ₆ H ₄ Cl	CO ₂ Bu ⁿ	30

^a Reaction conditions: bromobenzene (0.5 mmol), styrene (0.75 mmol), K₂CO₃ (1 mmol), NMP (1 mL), under Ar. ^b Isolated yield. ^c In these two reactions, 1 mol % of Pd(OAc)₂ and **2** were used. ^d 2.5 equiv of styrene was used, and 1,4-di(2-butylcarbonyl-*trans*-vinyl)benzene was isolated as the product. ^e No reaction was observed. ^f GC yield.

that Pd/**2** constituted a simple, yet efficient, catalyst system 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 TONs in most of the cases were about 10³, except for 2-bromopyridine where almost no reaction was observed. Besides aryl bromides, aryl iodides

could also be successfully used under the same reaction conditions. Nonetheless, Pd/**2** was not active enough to handle an aryl chloride unless it was activated by electron-withdrawing substituents (such as 4-COMe).

Having confirmed that **2** was a generally applicable ligand, we next went back to the question about the relative performance of **1**–**3**. Because the reaction yield could be a deceptive quantity, we decided to measure the reaction kinetics by monitoring the GC yields over certain period of time after the reaction was initiated. The detailed reaction conditions were as follows: bromobenzene = 10 mmol, styrene = 10 mmol, K₂CO₃ = 20 mmol, NMP = 10 mL, Pd(OAc)₂ = 0.001 mmol, ligand = 0.001 mmol, and temperature = 130 °C. In the first hour of the reaction, the amount of the *trans*-stilbene product was observed to increase in a linear fashion over time (see Figure 2). It was striking

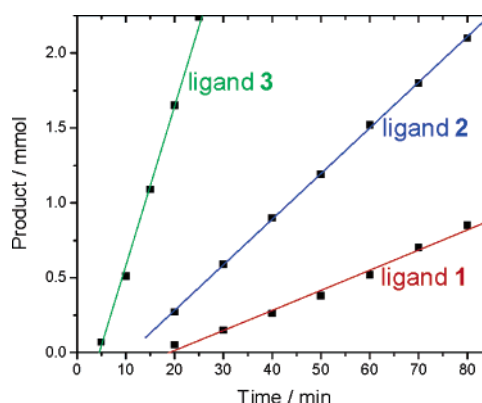


Figure 2. Initial velocity of the Heck reaction measured by GC.

to find that ligand **3** gave the fastest initial rate, followed by ligand **2**. Ligand **1** exhibited the slowest initial rate.

The above results illustrated complications in evaluating the Pd catalysts. Although ligand **3** was the most reactive, its overall performance (as assessed by the yield or TON) was the worst. On the other hand, the least reactive ligand (e.g., **1**) did not give the best overall performance either. To further understand the mechanistic basis for the different reactivities of ligands **1**–**3**, we decided to perform a theoretical study on the catalytic processes of the *N,O*-bidentate Pd complexes. Such a study has never been reported previously, but we considered it to be necessary at the present stage. To carry out the theoretical study, we hypothesized that the rate-determining step in the catalysis was the oxidative addition. The validity of this hypothesis was supported by previous calculations.²⁰ Furthermore, the fact that aryl chloride was not a good substrate must be due to the limiting difficulty of oxidative addition in the overall catalytic process.

Our calculations²¹ were performed using the B3PW91 method that was previously benchmarked for Pd chemistry.²²

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The geometry was optimized using the LANL2DZ basis set, while the energy calculations were performed using the LANL2DZ+p basis set. The solvent effect was taken into consideration by utilizing the PCM solvation model (solvent = NMP). The detailed results were shown in Figure 3. From

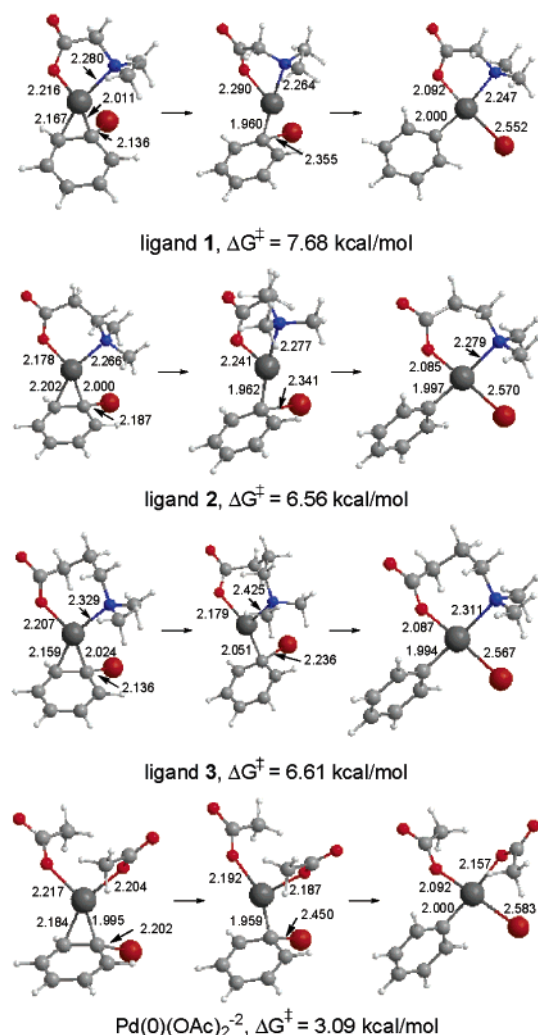


Figure 3. Structures of the starting material (left), transition state (middle), and product of oxidative addition (right).

the results it was found that ligand **1** gave the highest energy barrier for oxidative addition. The energy barrier of ligand **2** was about 1.1 kcal/mol lower than that of ligand **1**, in agreement with the faster initial rate observed for **2**. However, it was strange that the energy barrier of **3** was slightly higher than that of **2**. This appeared to be inconsistent with the observation that **3** led to the fastest initial rate.

To solve the puzzle, we further calculated the energy barrier of oxidative addition for Pd(0)(OAc)₂²⁻. It was found that without any other ligand, Pd(0) complexed with two acetate anions exhibited the lowest energy barrier. It is worth noting that a seven-membered ring must be formed in the

Pd complex with ligand **3**, which is a highly entropically unfavorable process. As a result, the resting state of the bidentate complex between ligand **3** and Pd is more likely to be a monoligated Pd species, where the free site can be occupied by an acetate anion. Accordingly, the catalytic performance of Pd(0)/**3** may resemble that of Pd(0)(OAc)₂²⁻. This would explain the much faster initial rate observed for ligand **3**.

Putting the experimental and theoretical results together, we came to the conclusion that both **1** and **2** can function as *N,O*-bidentate ligands for Pd catalysis. Ligand **2** is found to be better than **1** in overall performance, presumably because the oxidative addition facilitated by **2** is faster than that facilitated by **1**. Thus, if the Pd(0) complexes with **1** and **2** are of similar stability in the solution, the complex with **2** can produce more turnovers than that with **1** before Pd(0) eventually degrades. On the other hand, it is more likely that **3** functions as a monodentate ligand, which resembles a simple acetate anion. Ironically, the acetate anion is found to be the most powerful ligand for the oxidative addition to Pd(0).²³ However, the problem associated with the acetate ligand is the stability of the active monomeric Pd(0) species, which can aggregate to inactive Pd black.²⁴ Some sort of protection is required to sustain monomeric Pd(0). A monodentate N or O ligand (e.g., acetate or **3**) is probably not strong enough to provide such protection. As a result, it is more desirable to consider *N*- and/or *O*-bidentate ligands (e.g., **1** or **2**) where the chelation effect is expected to be beneficial.

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

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