Organic LETTERS

Letter

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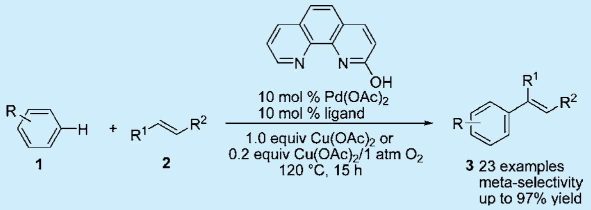
# 2-Hydroxy-1,10-phenanthroline vs 1,10-Phenanthroline: Significant Ligand Acceleration Effects in the Palladium-Catalyzed Oxidative Heck Reaction of Arenes

Cheng-Hao Ying, Shao-Bai Yan, and Wei-Liang Duan*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 LingLing Road, Shanghai 200032, China

Supporting Information

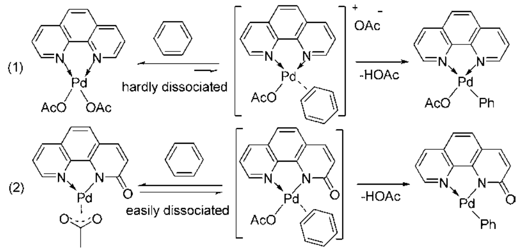
**ABSTRACT:** A series of bidentate monoanionic nitrogen ligands were designed and applied in the Pd-catalyzed oxidative Heck reaction of arenes with alkenes. Significant ligand-accelerated effects were observed, and direct C−H functionalized products were formed in high yields with meta-selectivity.



Ligand-accelerated catalysis is widely applied in various reactions, such as epoxidation, addition reactions, etc.[1] In such processes, efficiency and selectivity can be adjusted and controlled by appropriate ligand selection. By contrast, only a few suitable ligands can be utilized in palladium-catalyzed C−H functionalization reactions,[2−4] particularly for substrates without chelating groups. Usually, $Pd(OAc)_2$ or other simple palladium salts are the most widely used catalysts in such processes, and the addition of nitrogen ligands inhibits the catalytic activity of palladium catalyst. Only recently, Yu et al. and Sanford et al. reported that the use of monodentate pyridine-type ligands can increase the activity of the palladium catalysts in the C−H bond functionalization reactions of simple arenes.[5,6] Palladium ligated only to one nitrogen ligand is also reportedly important to the success of C−H activation reactions. Despite such impressive progress, the development of new ligands suitable for Pd-catalyzed C−H activation reactions remains challenging.

Bidentate nitrogen ligands such as 1,10-phenanthroline (1,10-phen) are seldom used in the palladium-catalyzed C−H activation reactions,[6] although it is a widely useful ligand for catalysis and for the preparation of various metal complexes.[7] 1,10-Phen coordinates with palladium acetate with square planar geometry, in which a Pd atom bonds covalently with two acetate anions.[8] We hypothesize that the inability of Pd/1,10-phen for C−H activation reaction may be due to the difficult dissociation of the acetate anion from the Pd atom to generate a vacant coordination site for an incoming simple arene (low coordinate ability without strong chelating groups) (Scheme 1, eq 1).[6] Based on this hypothesis, we envisioned that introducing a hydroxyl group at the 2-position of 1,10-phen to give a bidentate monoanionic nitrogen ligand 2-OH-1,10-phen would solve this problem. The complex of 2-OH-1,10-phen with $Pd(OAc)_2$ only has one acetate anion on the Pd atom. Given that the binding ability of acetic anion to Pd is not strong, a palladium intermediate having a vacant coordination site can be generated with relative ease and may be able to act as a catalyst for the C−H bond activation reaction (Scheme 1, eq 2). In the present work, we design and apply bidentate monoanionic nitrogen ligands for the Pd-catalyzed oxidative Heck reaction of simple arenes.

**Scheme 1. Basic Concept for Designing Bidentate Monoanonic Nitrogen Ligands in the C−H Activation Reactions of Arenes**

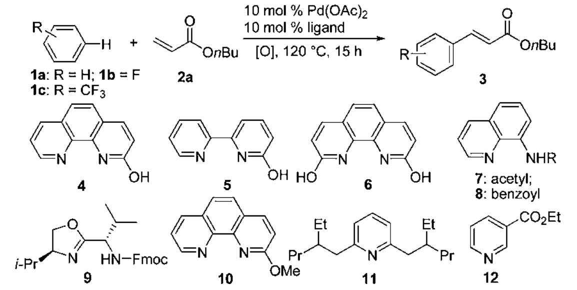


Fujiwara and Moritani reported the first Pd-catalyzed oxidative Heck reaction of simple arenes. Since then, major progress had been made.[9] However, most studies are still limited to electron-rich arenes.[10,11] A simple Pd salt without a ligand is inefficient for the direct olefination of electron-deficient arenes. Hence, we initially examined the oxidative Heck reactions of benzene and fluorobenzene with *n*-butyl acrylate in the presence of $Pd(OAc)_2$ and a series of nitrogen ligands (**4**−**10**). For the benzene substrate, the use of palladium acetate without ligand only afforded the product in 10% yield in the presence of $Cu(OAc)_2$ as oxidant (Table 1, entry 1). Interestingly, the addition of ligand **4**, 2-OH-1,10-phen, significantly increased the product yield to 97% (entry 2). In contrast, the use of 1,10-phen totally inhibited the progress of reaction with no formation of the desired product (entry 3). A

**Received:** November 21, 2013
**Published:** December 30, 2013

dx.doi.org/10.1021/ol4033804 | *Org. Lett.* 2014, 16, 500−503

Table 1. Palladium-Catalyzed Oxidative-Heck Reaction of Arenes with *n*-Butyl Acrylate[a]

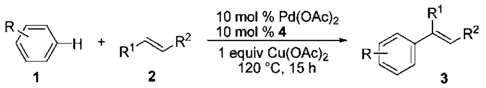


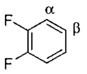
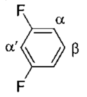
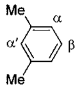
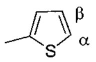
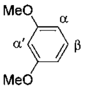
| entry | substrate | ligand | oxidant | yield[b] (%)/(ratio of *m*/*p*/*o*-isomers)[c] |
|---|---|---|---|---|
| 1 | **1a** |  | $Cu(OAc)_2$ | 10 |
| 2 | **1a** | **4** | $Cu(OAc)_2$ | 97 |
| 3 | **1a** | 1,10-Phen | $Cu(OAc)_2$ | 0 |
| 4 | **1b** |  | $Cu(OAc)_2$ | 6 |
| 5[d,e] | **1b** | **4** | $Cu(OAc)_2$ | 93 (4.9/1/1.6) |
| 6 | **1b** | 1,10-Phen | $Cu(OAc)_2$ | 0 |
| 7 | **1b** | **5** | $Cu(OAc)_2$ | 41 (3.7/1/1.2) |
| 8 | **1b** | **6** | $Cu(OAc)_2$ | 0 |
| 9 | **1b** | **7** | $Cu(OAc)_2$ | 45 (3.6/1.3/1) |
| 10 | **1b** | **8** | $Cu(OAc)_2$ | 0 |
| 11[e] | **1b** | **9** | $Cu(OAc)_2$ | 52 (1/0.9/5.8) |
| 12[e] | **1b** | **10** | $Cu(OAc)_2$ | 19 (2.1/1/3.2) |
| 13[e] | **1b** | **11** | $Cu(OAc)_2$ | 17 (1/2.4/6) |
| 14[e] | **1b** | **12** | $Cu(OAc)_2$ | 47 (1/1.9/7.5) |
| 15[e] | **1b** | Boc-L-valine | $Cu(OAc)_2$ | 63 (1/3.0/6.5) |
| 16[f] | **1c** | **4** | $O_2$ | 0 |
| 17[g] | **1b** | **4** | $Cu(OAc)_2$ | 0 |
| 18[h] | **1b** | **4** | $Cu(OAc)_2$ | 69 (4.6/1/1.3) |
| 19[i] | **1b** | **4** | $Cu(OAc)_2$ | 28 (3.7/1/1.9) |
| 20[j] | **1b** | **4** | $Cu(OAc)_2$ | 26 (5/1/3.2) |
| 21 | **1a** | **4** | BQ | 1 |
| 22 | **1a** | **4** | Tempo | 4 |
| 23 | **1a** | **4** | Oxone | 3 |
| 24 | **1a** | **4** | $CuCl_2$ | 0 |

[a] All the reactions were conducted with 0.20 mmol of alkenes in 3.0 mL of arenes. [b] Yields were determined by $^1H$ NMR analysis of the crude product using $CH_2Br_2$ as the internal standard. [c] The ratio of *m*/*p*/*o*-isomers was determined by $^1H$ NMR analysis of the crude product. [d] Isolated yield. [e] The ratio of *m*/*p*/*o*-isomers was determined by $^{19}F$ NMR analysis of the crude product. [f] Reaction conditions: 1 mL of trifluorotoluene, 0.20 mmol of **2a**, and 0.20 mmol of $Ac_2O$ in the presence of 10 mol % of $Pd(OAc)_2$ and 20 mol % of **4** under 1 atm of $O_2$ at 120 C, 15 h. [g] Without $Pd(OAc)_2$. [h] 5 mol % $Pd(OAc)_2$ used. [i] The reaction was conducted at 100 °C. [j] 10 mol % of $PdCl_2$ used.

similar ligand-accelerated effect was also observed for the reaction of fluorobenzene with *n*-butyl acrylate (entries 4−6), and a meta-product was preferentially formed. The more flexible 2-OH-1,1′-bipyridine **5** also exhibited moderate catalytic activity (entry 7). By contrast, ligand **6**[12] that contains two hydroxyl groups at the 2,9-positions of 1,10-phen did not catalyze this reaction (entry 8). Moreover, the easy-to-prepare ligand **7** bearing an acetyl group derived from 8-amino quinoline skeleton was also found to exhibit moderate accelerating activity (entry 9). However, ligand **8** that contains a benzoyl moiety was not effective (entry 10). In addition, FMOC-protected amino-oxazoline-based bidentate ligand **9**[13] also exhibits certain catalytic activity, but with ortho-selectivity (entry 11). Ligand **10** bearing a methyl group on the oxygen atom compared with ligand **4** only afforded the product in low yield (entry 12). This result seems to suggest the importance of the bidentate monoanionic framework of the ligand **4**. For comparison, monopyridine ligands **11**[5a] and **12**[9f] were examined under the current reaction conditions. Both of them afforded the ortho-functionalized compound preferentially (entries 13 and 14). Notably, Boc-protected L-valine featured as the L-X type ligand to transition metals[4] was demonstrated to afford the desired product in moderate yield, also with ortho-selectivity (entry 15). Using ligand **4**/$Pd(OAc)_2$ under Yu's conditions[5a] for the reaction of trifluorotoluene with **2a** did not produce the corresponding Heck product (entry

Table 2. Palladium-Catalyzed Oxidative-Heck Reaction of Arenes with Alkenes[a]



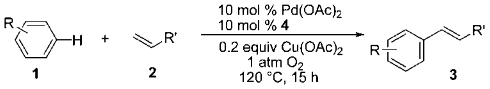
| entry | R | R¹ | R² | yield [%][b]/(ratio of *m*/*p*/*o*-isomers)[c] |
|---|---|---|---|---|
| 1 | F | H | $CO_2nBu$ | 93(4.9/1/1.6) |
| 2 | $CF_3$ | H | $CO_2nBu$ | 70(1.5/1/0) |
| 3 | $CO_2Me$ | H | $CO_2nBu$ | 97(3.6/1.7/1) |
| 4 | C(O)Me | H | $CO_2nBu$ | 79(2.7/1/1.6) |
| 5 | $NO_2$ | H | $CO_2nBu$ | 91(3.8/1/1) |
| 6 | CN | H | $CO_2nBu$ | 93(2.6/1/2.2) |
| 7[d] | Cl | H | $CO_2nBu$ | 84(3.0/1/1.6) |
| 8 | Br | H | $CO_2nBu$ | 75(3.6/1/1.4) |
| 9 |  | H | $CO_2nBu$ | 95(1.1/1)[e] |
| 10 |  | H | $CO_2nBu$ | 90(3.7/2/1.2)[f] |
| 11 | *p*-di-F | H | $CO_2nBu$ | 88 |
| 12 | F | H | $CO_2Et$ | 79(5.6/1/2.1) |
| 13 | F | H | $CO_2tBu$ | 85(4.4/1/1.4) |
| 14 | F | H | Ph | 97(6.2/1/2.6) |
| 15 | F | H | *p*-$MeOC_6H_4$ | 94(4.0/1/1.5) |
| 16 | F | H | *p*-$tBuC_6H_4$ | 76(2.0/0/1.0) |
| 17 | H | Ph | C(O)Ph | 69 |
| 18 | H | Ph | $CO_2Me$ | 42 |
| 19[g] | Me | H | $CO_2nBu$ | 80(17.5/7/1) |
| 20[h] | MeO | H | $CO_2nBu$ | 76(25/7/1) |
| 21 |  | H | $CO_2nBu$ | 82(1.2/1)[e] |
| 22[i] | *N*-methylindole | H | $CO_2nBu$ | 62[j] |
| 23[k] |  | H | $CO_2nBu$ | 36(1/10)[e] |
| 24 |  | H | $CO_2nBu$ | 49[l] |
| 25 | pyridine | H | $CO_2nBu$ | 27[m] |

[a] The reactions were conducted with 0.20 mmol of alkenes in 3.0 mL of arenes unless otherwise specified. [b] Isolated yield. [c] The ratio of *m*/*p*/*o*-isomers was determined by $^1H$ or $^{19}F$ NMR analysis of the isolated product. [d] 10 mol % of ligand **7** used. [e] The ratio of $\beta/\alpha$-isomers. [f] The ratio of $\beta/\alpha/\alpha'$-isomers. [g] 1.0 mL of toluene used. [h] 1 mL of anisole and 1 mL of EtOAc used. [i] 0.20 mmol of *N*-methylindole, 0.60 mmol of **2a** in 1 mL of dioxane. [j] Only the indole 3-isomer was formed. [k] 1 mL of 2-methylthiophene was used. [l] Only the $\beta$-isomer was formed. [m] Only the meta-isomer was formed.

16). These results indicated that ligand **4** possesses some particular properties for the current reaction with regard to the catalytic activity and regioselectivity. Finally, the screening of various oxidants, palladium precursors, temperature, and metal-to-ligand ratio revealed that 10 mol % $Pd(OAc)_2$ and **4** with 1 equiv of $Cu(OAc)_2$ at 120 °C were the optimum conditions (entries 17–24).

With the optimum conditions known, the substrate scope was then examined, and the results are shown in Table 2. Substrates having various electron-withdrawing groups, such as nitro-, ester-, nitrile-, chloro-, and bromo-moieties, can be tolerated to afford the corresponding products with good yields (Table 2, entries 1–11). With respect to the alkene counterparts, the acrylate, aryl-substituted ethylene also reacted with fluorobenzene smoothly, thereby furnishing the corresponding alkenes with good yields (entries 12–16). Furthermore, ethylcinnamic acid ester and chalcone containing substituted groups at the $\beta$-position can also be used in this protocol, furnishing $\beta,\beta$-diaryl-substituted acrylates or enones in moderate yields (entries 17 and 18). Electron-rich arenes have also been examined under the current conditions (entries 19–24). In sharp contrast to the reported system,[9d,e] the Heck products of toluene and anisole were obtained also with meta-selectivity (entries 19 and 20), which have not been reported to date. However, *N*-methylindole and 2-methylthiophene were functionalized at more electron-rich positions (entries 22 and 23). Notably, 1,3-dimethoxybenzene and pyridine[6a] were found to afford single regioisomers in moderate yields (entries 24 and 25). Molecular oxygen is regarded as an ideal oxidant in catalysis that enables a cleaner and more economical process.[14] Therefore, in the current catalytic system, oxygen (1 atm) was examined as an oxidant in the presence of 20 mol % of $Cu(OAc)_2$. An array of arenes can also be efficiently functionalized with alkenes with good yields (Table 3). It is worth mentioning that regioselectivities with catalytic $Cu(OAc)_2$ are different from that with stoichimetric $Cu(OAc)_2$. This observation may indicate that different oxidants or additives could be examined for further increasing the reaction selectivity.

Table 3. Palladium-Catalyzed Oxidative-Heck Reaction of Arenes with *n*-Butyl Acrylate Using Oxygen as the Oxidant

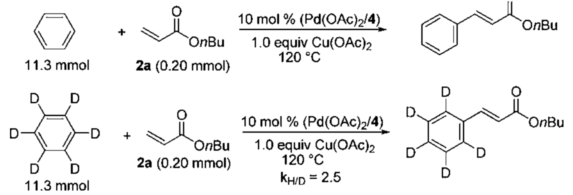


| entry | R | R′ | yield[a] (%)/(ratio of *m*/*p*/*o*-isomers)[b] |
|---|---|---|---|
| 1 | $CF_3$ | $CO_2$-*n*-Bu | 81 (1.5/1/0) |
| 2 | $CO_2Me$ | $CO_2$-*n*-Bu | 72 (5.5/2.5/1) |
| 3 | C(O)Me | $CO_2$-*n*-Bu | 86 (2/1/2.6) |
| 4 | $NO_2$ | $CO_2$-*n*-Bu | 61 (1.7/1/1) |
| 5 | CN | $CO_2$-*n*-Bu | 73 (2.1/1/1.3) |
| 6 | Br | $CO_2$-*n*-Bu | 80 (4.3/1.6/1) |

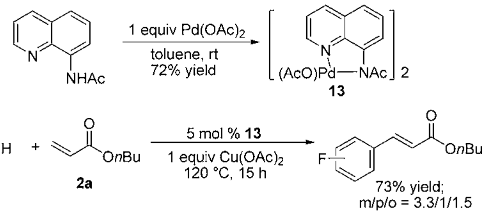
[a] Isolated yield. [b] The ratio of *m*/*p*/*o*-isomers was determined by $^1H$ or $^{19}F$ NMR analysis of the isolated product.

To gain further insight into the reaction mechanism in this catalytic system, the reaction of deuterated benzene with *n*-butyl acrylate was carried out to determine the kinetic isotope effect under standard conditions. A $K_H/K_D$ ratio of 2.5 was observed (Scheme 2, see the Supporting Information), and this value indicated that the C–H bond cleavage was involved in the rate-limiting step.[15] Attempts to identify the structure of palladium complex of ligand **4** with $Pd(OAc)_2$ were unsuccessful due to the very low solubility of the formed product in various solvents.[16] Alternatively, the ligand **7** reacted with palladium acetate smoothly, affording a palladium complex existing in dimeric form.[17] The use of the isolated complex for the reaction of fluorobenzene with *n*-butyl acrylate afforded the product in 73% yield (Scheme 3), which is higher than the yield obtained through in situ method. Competition experiments were also conducted between arenes having different electronic densities. Electron-rich arenes such as anisole or electron-poor arenes such as fluorobenzene, were found to both have lower reactivities than benzene (Scheme 4). Such trends in the reactivity of arenes could not be explained solely by concerted metalation-deprotonation (CMD)[18] or electrophilic aromatic substitution ($S_EAr$) pathways,[19] and the mechanism for the current system remains unclear.

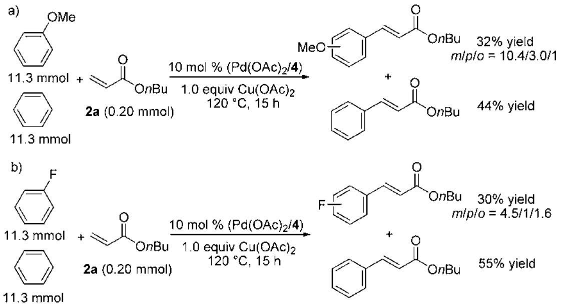
Scheme 2. Experiments with Isotopically Labeled Compounds



Scheme 3. Preparation of a Palladium Complex of Ligand 7 and Use in the Oxidative-Heck Reaction



Scheme 4. Intermolecular Competition Experiments with *n*-Butyl Acrylate



In summary, we have designed a series of bidentate monoanionic nitrogen ligands and used them in the Pd-catalyzed oxidative Heck reaction of simple arenes with mainly meta-selectivity in high yields. The characteristics of Pd catalyst coordinated with bidentate monoanionic ligands (i.e., having readily available vacant coordinated sites for incoming substrates) are the key factor affecting the success of C–H activation reactions. Attempts to further understand the reaction mechanism and applications of this catalytic system in other reactions are ongoing.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: wlduan@mail.sioc.ac.cn.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was financially supported by the National Basic Research Program of China (973 Program 2010CB833300), NSFC (20902099, 21172238), and SIOC. We thank Dr. Hao-Yang Wang for helping with MS analysis of the palladium complexes.

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