

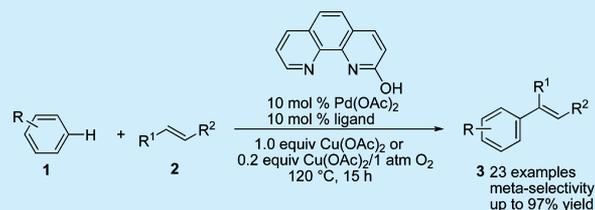
2-Hydroxy-1,10-phenanthroline vs 1,10-Phenanthroline: Significant Ligand Acceleration Effects in the Palladium-Catalyzed Oxidative Heck Reaction of Arenes

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S Supporting Information

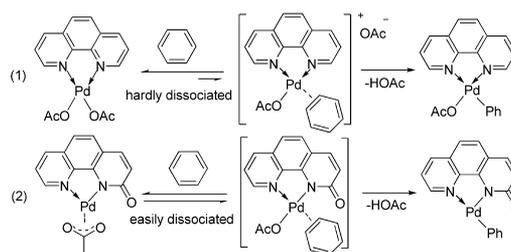
ABSTRACT: A series of bidentate monoanionic nitrogen ligands were designed and applied in the Pd-catalyzed oxidative Heck reaction of arenes with alkenes. Significant ligand-accelerated effects were observed, and direct C–H functionalized products were formed in high yields with meta-selectivity.



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

Scheme 1. Basic Concept for Designing Bidentate Monoanionic Nitrogen Ligands in the C–H Activation Reactions of Arenes



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.

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

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

entry	substrate	ligand	oxidant	yield ^b (%) / (ratio of <i>m/p/o</i> -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

^aAll the reactions were conducted with 0.20 mmol of alkenes in 3.0 mL of arenes. ^bYields were determined by ¹H NMR analysis of the crude product using CH₂Br₂ as the internal standard. ^cThe ratio of *m/p/o*-isomers was determined by ¹H NMR analysis of the crude product. ^dIsolated yield. ^eThe ratio of *m/p/o*-isomers was determined by ¹⁹F NMR analysis of the crude product. ^fReaction conditions: 1 mL of trifluorotoluene, 0.20 mmol of 2a, and 0.20 mmol of Ac₂O in the presence of 10 mol % of Pd(OAc)₂ and 20 mol % of 4 under 1 atm of O₂ at 120 °C, 15 h. ^gWithout Pd(OAc)₂. ^h5 mol % Pd(OAc)₂ used. ⁱThe reaction was conducted at 100 °C. ^j10 mol % of PdCl₂ 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 6¹² 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 9¹³ 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 metals⁴ 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

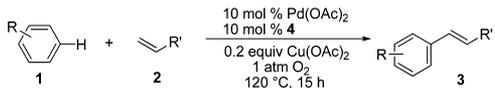
entry	R	R ¹	R ²	yield [%] ^b / (ratio of <i>m/p/o</i> -isomers) ^c
1	F	H	CO ₂ <i>n</i> Bu	93(4.9/1/1.6)
2	CF ₃	H	CO ₂ <i>n</i> Bu	70(1.5/1/0)
3	CO ₂ Me	H	CO ₂ <i>n</i> Bu	97(3.6/1.7/1)
4	C(O)Me	H	CO ₂ <i>n</i> Bu	79(2.7/1/1.6)
5	NO ₂	H	CO ₂ <i>n</i> Bu	91(3.8/1/1)
6	CN	H	CO ₂ <i>n</i> Bu	93(2.6/1/2.2)
7 ^d	Cl	H	CO ₂ <i>n</i> Bu	84(3.0/1/1.6)
8	Br	H	CO ₂ <i>n</i> Bu	75(3.6/1/1.4)
9		H	CO ₂ <i>n</i> Bu	95(1.1/1) ^e
10		H	CO ₂ <i>n</i> Bu	90(3.7/2/1.2) ^f
11	<i>p</i> -di-F	H	CO ₂ <i>n</i> Bu	88
12	F	H	CO ₂ Et	79(5.6/1/2.1)
13	F	H	CO ₂ <i>t</i> Bu	85(4.4/1/1.4)
14	F	H	Ph	97(6.2/1/2.6)
15	F	H	<i>p</i> -MeOC ₆ H ₄	94(4.0/1/1.5)
16	F	H	<i>p</i> - <i>t</i> BuC ₆ H ₄	76(2.0/0/1.0)
17	H	Ph	C(O)Ph	69
18	H	Ph	CO ₂ Me	42
19 ^g	Me	H	CO ₂ <i>n</i> Bu	80(17.5/7/1)
20 ^h	MeO	H	CO ₂ <i>n</i> Bu	76(25/7/1)
21		H	CO ₂ <i>n</i> Bu	82(1.2/1) ^e
22 ⁱ	<i>N</i> -methylindole	H	CO ₂ <i>n</i> Bu	62 ^j
23 ^k		H	CO ₂ <i>n</i> Bu	36(1/10) ^e
24		H	CO ₂ <i>n</i> Bu	49 ^l
25	pyridine	H	CO ₂ <i>n</i> Bu	27 ^m

^aThe reactions were conducted with 0.20 mmol of alkenes in 3.0 mL of arenes unless otherwise specified. ^bIsolated yield. ^cThe ratio of *m/p/o*-isomers was determined by ¹H or ¹⁹F NMR analysis of the isolated product. ^d10 mol % of ligand 7 used. ^eThe ratio of *β/α*-isomers. ^fThe ratio of *β/α/α'*-isomers. ^g1.0 mL of toluene used. ^h1 mL of anisole and 1 mL of EtOAc used. ⁱ0.20 mmol of *N*-methylindole, 0.60 mmol of 2a in 1 mL of dioxane. ^jOnly the indole 3-isomer was formed. ^k1 mL of 2-methylthiophene was used. ^lOnly the *β*-isomer was formed. ^mOnly 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 β-position can also be used in this protocol, furnishing β,β-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

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



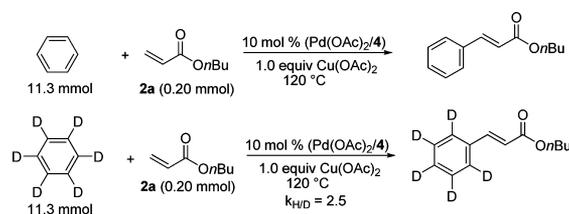
entry	R	R'	yield ^a (%) / (ratio of <i>m/p/o</i> -isomers) ^b
1	CF ₃	CO ₂ - <i>n</i> -Bu	81 (1.5/1/0)
2	CO ₂ Me	CO ₂ - <i>n</i> -Bu	72 (5.5/2.5/1)
3	C(O)Me	CO ₂ - <i>n</i> -Bu	86 (2/1/2.6)
4	NO ₂	CO ₂ - <i>n</i> -Bu	61 (1.7/1/1)
5	CN	CO ₂ - <i>n</i> -Bu	73 (2.1/1/1.3)
6	Br	CO ₂ - <i>n</i> -Bu	80 (4.3/1.6/1)

^aIsolated yield. ^bThe ratio of *m/p/o*-isomers was determined by ¹H or ¹⁹F NMR analysis of the isolated product.

worth mentioning that regioselectivities with catalytic Cu(OAc)₂ are different from that with stoichiometric Cu(OAc)₂. This observation may indicate that different oxidants or additives could be examined for further increasing the reaction selectivity.

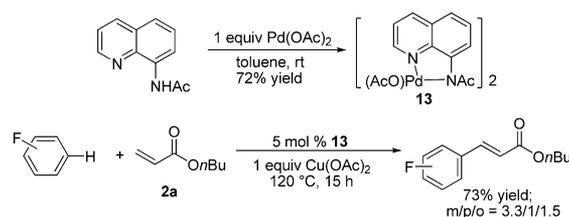
To gain further insight into the reaction mechanism in this catalytic system, the reaction of deuterated benzene with *n*-butyl acrylate was carried out to determine the kinetic isotope effect under standard conditions. A *K*_H/*K*_D ratio of 2.5 was observed (Scheme 2, see the Supporting Information), and this value indicated that the C–H bond cleavage was involved in the rate-limiting step.¹⁵ Attempts to identify the structure of

Scheme 2. Experiments with Isotopically Labeled Compounds



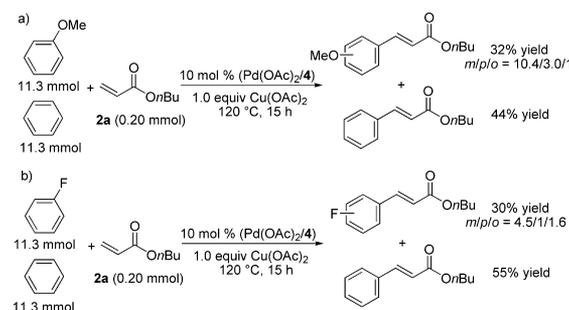
palladium complex of ligand **4** with Pd(OAc)₂ were unsuccessful due to the very low solubility of the formed product in various solvents.¹⁶ Alternatively, the ligand **7** reacted with palladium acetate smoothly, affording a palladium complex existing in dimeric form.¹⁷ The use of the isolated complex for the reaction of fluorobenzene with *n*-butyl acrylate afforded the product in 73% yield (Scheme 3), which is higher than the yield

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



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

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



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.

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>.

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Notes

The authors declare no competing financial interest.

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