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Pd-Diimine: A Highly Selective Catalyst System for the Base-Free Oxidative Heck Reaction

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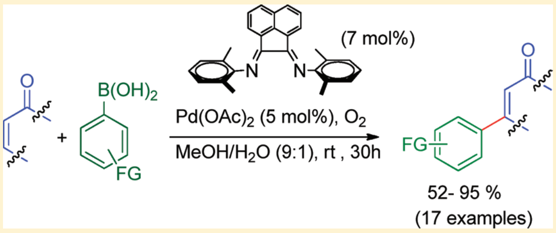
Supporting Information

ABSTRACT: $Pd(OAc)_2$/**3** is an efficient catalyst system for the base-free oxidative Heck reaction that outperforms the currently available catalysts for the more challenging substrates studied. The catalyst system is highly selective, and works at room temperature with dioxygen as the oxidant.



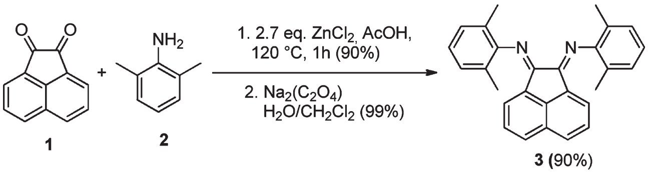
The oxidative variant of the Heck reaction[1] has gained considerable significance in recent years. Though first reported by Heck as early as 1969 with organomercurials,[2] this reaction failed to catch broad interest until the group of Uemura[3] pioneered the use of boronic acids, sparking a wave of developments. Pivotal contributions by the groups of Larhed[4] and Jung,[5] among others, considerably simplified the reaction system by eliminating the need for base, use of molecular oxygen as the sole oxidant, and by performing the reaction at room temperature. These mild conditions, accompanied by the commercial availability of functionalized boronic acids, make this reaction a valuable alternative for the classical Mizoroki–Heck reaction.

In our studies on the closely related Pd-catalyzed conjugate addition of boronic acids[6] and siloxanes,[7] we became aware of the challenge to obtain either the Heck or the conjugate addition product selectively. Cyclohex-2-en-1-one is a typical example of a substrate where mixtures are commonly noticed.[8] Therefore we aimed to develop a highly efficient catalyst for the more challenging substrates in the oxidative Heck reaction using a procedure that is mild and easy to operate.

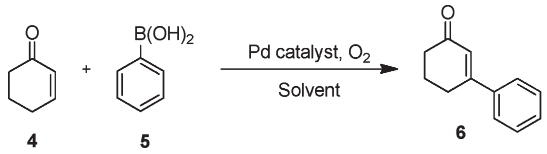
The currently used ligands for the oxidative Heck reaction are comprised of bipyridine, 1,10-phenanthroline, and especially 2,9-dimethyl-1,10-phenanthroline, known as "dmphen" or neocuproine. Although readily available, the former two ligands have the tendency to form inactive PdL_2 complexes and the stability of dmphen ligands under oxidative conditions is uncertain.[9]

Bis-imines of acenaphthenequinone, so-called BIAN ligands (**3**), have been applied in palladium-catalyzed polymerizations[10] and hydrogenations.[11] In addition to their convenient synthesis[12] (Scheme 1), BIAN ligands satisfy the required criteria, namely robust palladium complex formation, steric bulk discouraging dimerization, and resistance toward oxidation.[13]

Scheme 1. Synthesis of BIAN Ligand (3)



Cyclohex-2-en-1-one (**4**) was chosen as the test substrate in the oxidative Heck reaction with phenylboronic acid (**5**) because this normally leads to poor selectivities along with the reduced Heck product, phenol, and biphenyl.[14] Oxygen atmosphere and room temperature were set as important criteria for the reaction.



We started our study by optimization of the solvent. DMF and MeOH gave full conversion to the product overnight. Varying amounts of boroxine were observed when using dry methanol, which was avoided by using a 9:1 (v/v) mixture of MeOH/water. Surprisingly, EtOH, THF, or THF/water (2:1) resulted in incomplete conversion.

To determine the catalytic activity of the $Pd(OAc)_2$/**3** complex, a series of experiments were performed (Table 1) with and without the ligand, and in comparison with dmphen. $Pd(OAc)_2$ resulted in only 50% conversion and large amounts of biphenyl

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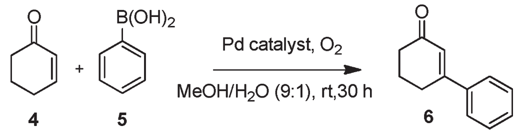
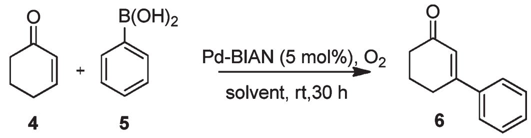
Table 1. Catalyst Screening[a]



entry	$Pd(OAc)_2$ (mol %)	ligand (mol %)	conversion[b]	side products
1	5		50%	biphenyl (50%)
2	5	**3** (5)	full	biphenyl (5%)
3	5	**3** (7)	full	
4	5	**3** (15)	full	
5	5	dmphen (5)	40%	biphenyl (30%)
6	5	dmphen (15)		
7		**8a** (5)	full	biphenyl (5%)
8		**7a** (5)	80%	biphenyl (10%)

[a] Reagents and conditions: Cyclohex-2-en-1-one (0.1 mmol), phenylboronic acid (0.15 mmol), O_2, rt, MeOH/water (9:1), 30 h. dmphen = 2,9-dimethyl-1,10-phenanthroline. [b] Determined by GC with dodecane as internal standard.

Table 2. Optimization of Reaction Parameters



entry	**8a** (mol %)	ratio (**4**:**5**)	solvent	atm	*t* (h)	yield[a] (%)
1	5	1:3.0	MeOH (dry)	O_2[c]	24	75
2	5	1:2.5	MeOH/H_2O (9:1)	O_2[c]	28	86
3	5	1:1.5	MeOH/H_2O (9:1)	O_2[c]	30	85
4	2.5	1:1.5	MeOH/H_2O (9:1)	O_2[c]	45	77
5	1	1:1.5	MeOH/H_2O (9:1)	O_2[c]	72	nd[b]
6	5	1:1.5	MeOH/H_2O (9:1)	air	30	45
7	5	1:1.5	MeOH/H_2O (9:1)	air[c]	30	49
8	5	1:1.5	MeOH/H_2O (9:1)	air[d]	30	50

[a] Isolated yield. [b] Not determined. [c] Balloon pressure. [d] 2 atm.

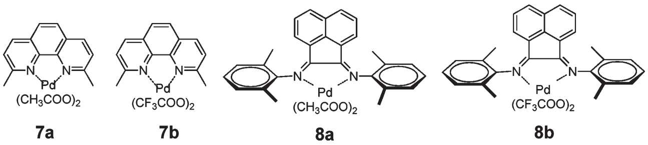


Figure 1. Pd(II) complexes studied.

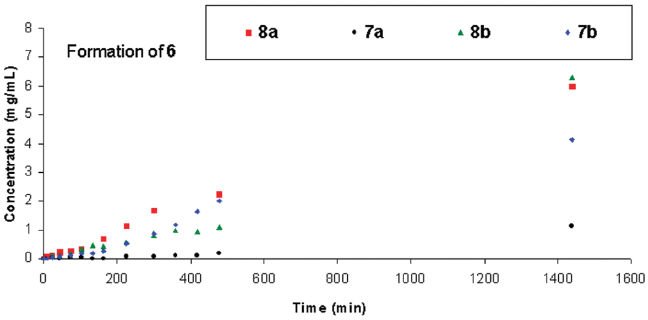


Figure 2. Product (**6**) formation with **7a**, **7b**, **8a**, and **8b** over time.

(entry 1). We were pleased to see that addition of 5 mol % of **3** (entry 2) gave full conversion with still a small amount of biphenyl formed, while 7 mol % led to selective product formation (entry 3). In addition, the formation of phenol or benzene as side products was reduced to minute traces. Using a larger excess of the ligand (entry 4) did not affect the conversion or selectivity. This is an important advantage of the use of **3**, as a small excess of ligand can ligate any free palladium formed, and any Pd(**3**)$_2$ species, if formed, does not compromise the activity. Dmphen (5 mol %), on the other hand, resulted in only 40% conversion under the same conditions (entry 5) while a complete loss of activity was observed with 15 mol % (entry 6), probably due to coordinative saturation. Preformed $Pd(OAc)_2$/**3** (**8a**) led to similar results as the in situ formed complex (entries 2 and 7) while preformed $Pd(OAc)_2$/dmphen (**7a**) gave 80% conversion. Apparently, with dmphen, catalyst formation in solution is slow or incomplete although a 30 min activation time was applied before starting the reaction.

Initially, 3.0 equiv of phenylboronic acid were necessary to obtain full conversion under ambient conditions, with dry methanol as the solvent (Table 2, entry 1). However, only 1.5 equiv was sufficient (entry 3) to obtain full conversion in a 9:1 (v/v) mixture of MeOH/water, though this led to a slight increase in reaction time from 1 day to 30 h.

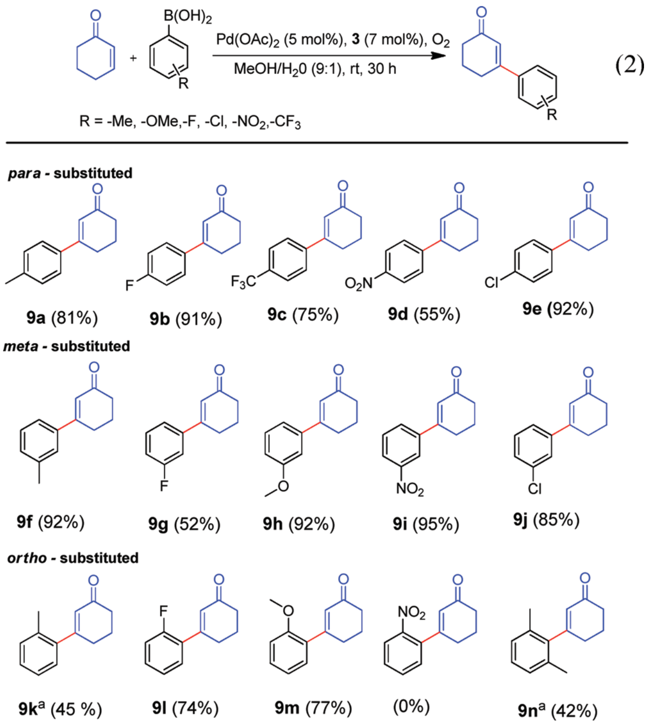
Lowering the catalyst loading to 2.5 mol % (entry 4) increased the reaction time to 45 h, while the reaction was incomplete even after 72 h with 1 mol % of the catalyst (entry 5). To determine whether air could be used instead of pure dioxygen, the reaction vessel was left open to air. The reaction was found to proceed (entry 6) albeit with lower yield. Air at balloon pressure (entry 7) or at 2 atm (entry 8) did not result in a significant improvement.

Thus, the optimal conditions for the reaction are a 9:1 MeOH/water mixture as solvent at room temperature and with dioxygen. In situ catalyst formation with a slight excess of ligand (7 mol % of **3** to 5 mol % of $Pd(OAc)_2$) was found to give the highest yield (86%)[15] and full selectivity.

Four complexes, **7a**, **7b**, **8a**, and **8b** (Figure 1), were earmarked to study the conversion and biphenyl formation in time (Figure 2) under the optimized conditions. Trifluoroacetate complexes, **7b** and **8b**, were chosen to investigate the influence of the counterion for the reaction, as the anion has been proposed to participate in the regeneration of the active catalyst from the peroxoboronate species in the mechanism put forth by Jung et al.[5d]

Product formation in time, determined by GC with use of complexes **7a**, **7b**, **8a**, and **8b**, is presented in Figure 2.[16] The key to the improved selectivity and activity of the BIAN-based catalyst turned out to be the enhanced initial rate of the reaction. The time profiles show a fast initiation of the oxidative Heck reaction, and minimal biphenyl formation with $Pd(OAc)_2$/**3** as the catalyst. Interestingly, no activation period was observed for the reaction. GC-detectable quantities of biphenyl were formed at the beginning of the reaction, presumably en route to the formation of the active species.[16] However, the biphenyl concentration remained unchanged in time for BIAN complexes **8a** and **8b**, while an increase was observed with **7a** and **7b**. Correlating this result with entries 1 and 2 from Table 1, it is concluded that very little Pd remains unligated in the case of Pd-BIAN. With complexes **7a** and **7b**, the rate of biphenyl formation

Scheme 2. Boronic Acids Used in the Oxidative Heck Reaction[b]



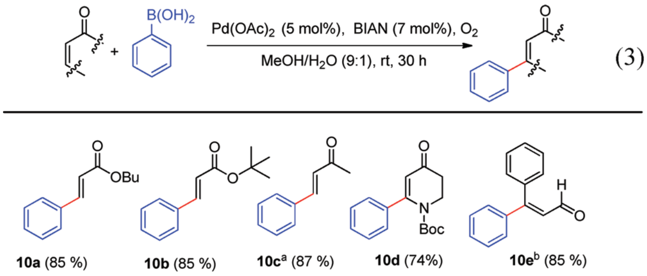
[a] Heated to reflux. [b] Reagents and conditions: $Pd(OAc)_2$ (5 mol %), **3** (7 mol %), cyclohex-2-en-1-one (1 mmol), boronic acid (1.5 mmol), O_2, 2 mL of MeOH/water (9:1), rt, 30 h. Isolated yields.

was found to supersede product formation, resulting in a poor overall selectivity for the reaction. **8a** and **8b** showed comparable activity, but a compelling difference was observed between **7a** and **7b**. Apparently, either the active catalyst formation is different for dmphen and **3**, or the reactions have a different rate determining step.

So, on one hand the use of $Pd(O_2CCF_3)_2$ in combination with dmphen (**7b**) leads to a considerably improved catalyst compared to the reported $Pd(OAc)_2$/dmphen combination (**7a**), and on the other hand the BIAN-based catalysts **8a** and **8b** outperform the dmphen-based catalysts (Figure 2).

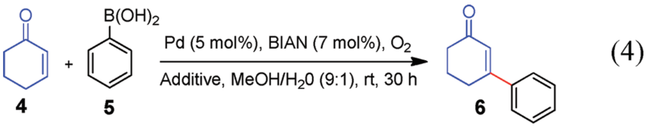
Equipped with the knowledge that complexes **8a** and **8b** are efficient catalysts, and the fact that in situ formed **8a** is slightly more efficient than the preformed catalyst, we proceeded to explore the scope and limitations of our system. To understand the influence of steric and electronic factors on the reaction, a variety of substituted boronic acids was chosen (eq 2, Scheme 2). In general, meta- and para-substituted phenylboronic acids give high to excellent yields. The highest yield (**9i**, 95%) was obtained with *m*-nitrophenylboronic acid, but also *m*-tolyl-, *m*-anisyl-, *p*-chloro-, and *p*-fluorophenylboronic acid gave the corresponding Heck products **9f**, **9h**, **9e**, and **9b** in yields exceeding 90%. Good yields of **9a**, **9c**, **9j**, and **9g** were obtained with *p*-tolyl-, *p*-trifluoromethyl-, *m*-chloro-, and *m*-fluorophenylboronic acids, respectively. As expected, ortho-substituted phenylboronic acids gave lower yields compared to meta- or para-substituted boronic acids bearing the same functional group (except **9l**), irrespective of the electronic factors. However, even *o*-tolyl, and the sterically demanding *o*,*o*′-xylyl boronic acid were found to react at reflux temperature to afford the corresponding Heck products, **9k** and **9n**, in moderate yields. *O*-Nitrophenylboronic acid did not react even upon reflux. The scope of the reaction with regard to various Michael acceptors was also investigated (Scheme 3). Acrylates afforded the corresponding Heck products **10a** and **10b** in a high yield (85%). Due to its volatility, a 2-fold excess of methylvinyl ketone with respect to phenylboronic acid was employed to furnish **10c** in high yield (87%).

Scheme 3. Scope of Enones[c]



[a] Methylvinyl ketone (2 mmol), phenylboronic acid (1 mmol) used. [b] Heated to reflux. [c] $Pd(OAc)_2$ (5 mol %), **3** (7 mol %), enone (1 mmol), phenylboronic acid (1.5 mmol), O_2, 2 mL of MeOH/H_2O (9:1), rt, 30 h. Isolated yields.

Table 3. Addition of Halide Salts[a]



entry	additive	quantity	conversion (%)
1	LiCl	10 equiv	<2
2	LiCl	1 equiv	<2
3	LiCl	5 mol %	80
3	LiBr	1 equiv	<2
4	$ZnCl_2$	1 equiv	<2
5	Bu_4NCl	1 equiv	<2
6	$Zn(OTf)_2$	1 equiv	74
7	Li(OTf)	1 equiv	78

[a] Determined by GC, with dodecane as internal standard.

Boc-protected 2,3-dihydropyridin-4(1*H*)-one, an important building block for alkaloid synthesis,[17] gave the corresponding Heck product **10d** in good yield (74%). We were pleased to learn that even cinnamaldehyde underwent the oxidative Heck reaction with high yield of 85% (**10e**). This bears significance, as aldehydes are often unstable under standard Mizoroki–Heck conditions, i.e. the presence of base and high temperature, where they tend to decompose or provide aldol products.[18] Interestingly, most of the compounds described here have not been previously synthesized by either Mizoroki–Heck or oxidative Heck procedures, and have only been observed occasionally as side products in conjugate addition reactions.

We were intrigued by the observation that $Pd(OAc)_2$/**3** gives high yields in the oxidative Heck reaction also when electron poor phenylboronic acids are employed. On the basis of observations and DFT calculations, Larhed and co-workers[4c,e] proposed that a cationic intermediate is pertinent with bis-nitrogen ligated Pd species in the oxidative Heck reaction.

Concomitantly, the addition of an excess of halide salts to the reaction system was found to retard the reaction, by forming a stable Pd-halide complex that is inactive in catalysis. As a consequence of this proposed cationic intermediate, electron deficient boronic acids are expected to result in poor conversions, which is found by using dmphen as the ligand.

Also, in our hands, the addition of halide salts resulted in a dramatic drop in reactivity of the catalyst, irrespective of the cation (Table 3). A large excess of LiCl inhibited the formation of **6** completely, even at reflux (entry 1). When 1 equiv of LiCl with respect to the substrate was added, the reaction was retarded at rt (entry 2), but proceeded with moderate conversion at reflux. Five mol % (1 equiv with respect to Pd) of LiCl did not hinder the reaction at all (entry 3). When salts without halides were added, the catalytic activity was unaffected (entries 6 and 7). It remains therefore unexplained why on one hand electron poor arylboronic acids react well in the Pd-BIAN catalyzed oxidative Heck reaction whereas on the other hand a cationic intermediate is most probably involved.

In summary, $Pd(OAc)_2$/**3** is an excellent catalyst for the base-free oxidative Heck reaction of arylboronic acids at room temperature. The mild reaction conditions permit the use of a diverse range of boronic acids and Michael acceptors, including aldehydes. Kinetic data show the high selectivity and reaction rate of BIAN ligand **3** compared to commonly used catalysts like 2,9-dimethylphenanthroline (dmphen). This study represents a novel and selective route to many of the described compounds, as most of them have not been synthesized by Heck procedures previously, and are only observed as side products. Studies to broaden the scope of this catalyst type are currently underway.

EXPERIMENTAL SECTION

Representative Procedure:

Synthesis of 3-Phenylcyclohex-2-enone (6) To a Schlenk tube equipped with a magnetic stirring bar and a septum was added palladium acetate (11 mg, 5 mol %, 0.05 equiv) and BIAN (28 mg, 7 mol %, 0.07 equiv). The mixture was dissolved in 2 mL of a solution of $MeOH/H_2O$ (9:1) and stirred for 30 min at 20 °C, followed by the addition of the cyclohex-2-en-1-one **4** (97 μL, 1.0 mmol, 1.0 equiv) and phenyl boronic acid **5** (183 mg, 1.5 mmol, 1.5 equiv). The Schlenk tube was flushed with O_2 and connected to an O_2 balloon. The reaction mixture was allowed to stir at 20 °C; when the reaction was judged complete (by TLC, GC), the reaction was stopped. The reaction mixture was concentrated in vacuo and loaded directly on the column, and the desired product, **6** (147 mg, 0.85 mmol, 85%), was isolated as a off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.34 (m, 5H), 6.38 (s, 1H), 2.73 (t, J = 6.0 Hz, 2H), 2.44 (t, J = 6.7 Hz, 2H), 2.10 (t, J = 6.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.8, 159.8, 138.8, 130.0, 128.8, 126.1, 125.4, 37.3, 28.1, 22.1. Calcd mass for $[M + H]^+$ 173.0961, found $[M + H]^+$ 173.0960.

ASSOCIATED CONTENT

Ⓢ Supporting Information. Detailed experimental procedures and spectroscopic and characterization data of all the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The yields reported in this article are calculated based on cyclohex-2-en-1-one, the limiting reagent. These are, therefore, higher than those reported in ref 5d, where they are calculated based on the boronic acid.

(16) For detailed time-profiles of each of the complexes, see the Supporting Information.

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