Oxime-Derived Palladium Complexes as Very Efficient Catalysts for the Heck–Mizoroki Reaction

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Abstract: Oxime-derived, chloro-bridged palladacycles **16** are efficient complexes for the Heck vinylation of aryl halides. The isolated catalysts are thermally stable, not sensitive to air or moisture and easily accessible from inexpensive starting materials. The reaction can be performed under aerobic conditions, with aryl iodides, bromides and chlorides with acrylic esters and olefins displaying turnover numbers (TON) of up to 10^{10} for phenyl iodide and turnover frequencies (TOF) of 1.4×10^8 h^{-1}. Deactivated aryl bromides undergo the Heck reaction with styrene with TON and TOF values up to 97,000 and 6063 h^{-1}, respectively. Even aryl chlorides undergo the coupling reaction with olefins with TON up to 920. Complexes **16** catalyze the synthesis of 2,3-disubstituted indenones and indoles in good yields via annulation reaction of internal alkynes with *o*-bromo- or *o*-chlorobenzaldehyde and *o*-iodoaniline, respectively.

Keywords: catalysts; C-C coupling; metallacycles; N ligands, palladium.

Introduction

The palladium-catalyzed reaction of organic halides with alkenes (the Heck–Mizoroki reaction[1]) has become one of the best methods for carbon-carbon bond formation in organic synthesis.[2]. During the last few years, very active systems have been developed in order to improve both stability and efficiency of palladium-based catalysts. These new systems are capable of achieving extremely high catalytic activities even with fairly unreactive aryl bromides and chlorides. For example, noteworthy advances have been described by using sterically hindered, electron-rich phosphanes,[3] tetraphenylphosphonium salts in combination with *N*,*N*-dimethylglycine (DMG),[4] and even under phosphine-free conditions.[5] However, lately, palladacycles have been by far the most developed and studied Heck-type catalysts as they are presently the most successful and, because of their structural versatility and easy synthetic accessibility, most promising catalysts in C-C bond forming reactions.[6] Among them, phospha-palladacycles **1**,[6c,7] **2**,[8] **3**[9] developed by Herrmann, Milstein and Shaw, respectively, have been demonstrated to be excellent catalysts for these types of processes (Figure 1). *ortho*-Palladated triaryl phosphites **4**[10] and **5**[11] and phosphinite **6**,[12] where ligand strength has been decreased, have markedly higher activity than their phosphino analogues. Finally, phosphine-free heterocyclic carbenes **7**,[6c,13] **8**,[14] **9**,[15] and **10**,[16] *ortho*-metallated benzyl thioethers **11**[17] and **12**,[17b] benzyl ethers **13**,[18] and cyclometallated imine-type derivatives **14**[19] and **15**[20] have been found to be stable but still very active catalysts in Heck reactions with TONs (turnover number = mol product mol Pd^{-1}) up to 10^5-10^6. All these cyclometallated compounds exhibit higher thermal stability compared with conventional Pd(0) catalysts and can operate through a Pd^{II}-Pd^{IV} or Pd^0-Pd^{II} mechanism.[21]

Very recently, as part of our studies to find robust and easily prepared systems to catalyze C-C bond-forming reactions, we found that oxime-based palladacycles **16** are very efficient and versatile catalysts for a wide range of useful and well known C-C coupling processes[22] such as Heck, Suzuki, Stille, Sonogashira and Ullmann reactions. These catalysts are very thermally and air stable and showed TONs up to 10^4 for the Heck coupling of aryl iodides with methyl acrylate. In this paper, we report on the evaluation and optimization of the Heck coupling of aryl halides such as iodides, bromides and chlorides and different olefins with oxime-derived palladacycles as catalysts[23,24] and also in cycloannulation reactions with internal alkynes.

Results and Discussion

Synthesis of Oxime-Derived Palladium Complexes

For the preparation of the metallated complexes **16a – d**, **17** and **18** different aliphatic and aromatic oximes **19** derived from acetophenone, benzophenone, 4,4′-dime-

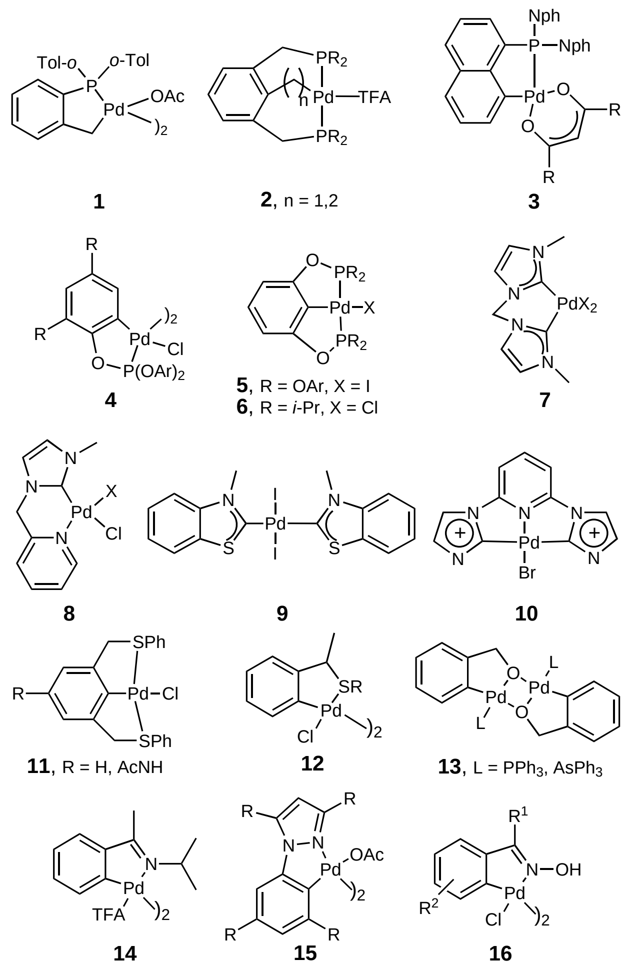
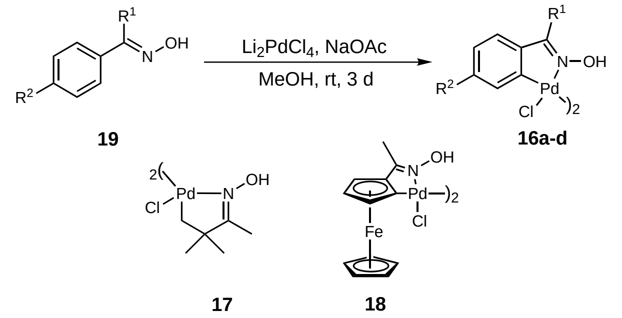
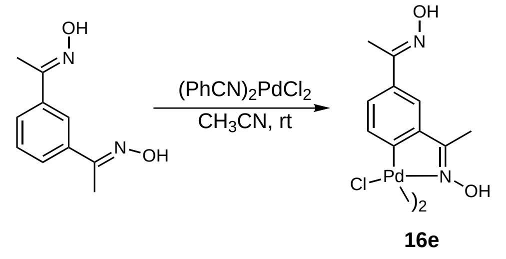


Figure 1.



Scheme 1.



Scheme 2.

thoxybenzophenone, 4,4′-dichlorobenzophenone, pinacolone and acetylferrocene, were synthesized and carbopalladated[25,26] with lithium tetrachloropalladate (Li_2PdCl_4) in MeOH in the presence of NaOAc as base at room temperature to provide chloro-bridge complexes **16a – d**, **17**, and **18** in high yields (Scheme 1, Table 1).

Searching for tridentate NCN pincer-type catalysts, the palladation of 1,3-diacetylbenzene dioxime (Table 1, entry 5), had to be performed with bis(benzonitrile)dichloropalladium(II) [$(PhCN)_2PdCl_2$] in acetonitrile at room temperature and in the absence of base. However, it was found to lead exclusively to the formation of the monopalladated dimeric complex **16e** in a 40% isolated yield[27] (Scheme 2).

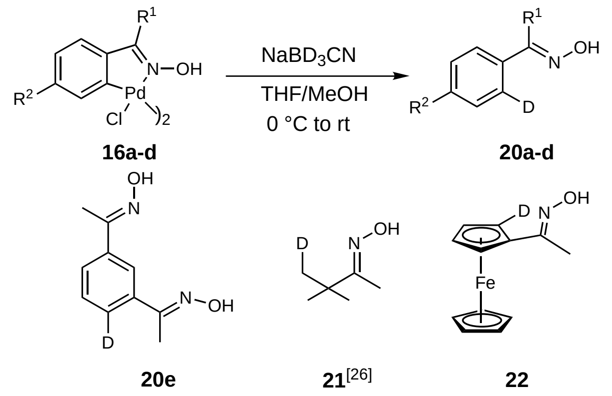
All these palladacycles have been fully characterized and have shown satisfactory IR, ^{1}H, and ^{13}C NMR spectra (see Experimental Section). Their reduction with deuterated sodium cyanoborohydride ($NaBD_3CN$),[26] led to the expected Pd-D exchange affording the deuterated oximes **20a – e**, **21**, and **22** in high yields (Scheme 3).

However, metallation of fluorenone oxime, with Li_2PdCl_4 did not led to the corresponding cyclopalla-

Table 1. Synthesis of palladacycles **16 – 18**.

Entry	No.	R^1	R^2	Yield [%][a]	mp [°C]
1	**16a**	Me	H	92	209 – 212[b]
2	**16b**	Ph	H	64	139 – 141[c]
3	**16c**	p-MeOC$_6$H$_4$	MeO	92	135 – 137
4	**16d**	p-ClC$_6$H$_4$	Cl	95	208 – 210
5	**16e**	Me	4-C(CH$_3$) = NOH	40	> 320
6	**17**	pinacolone		60	152[d]
7	**18**	acetylferrocene		75	> 320

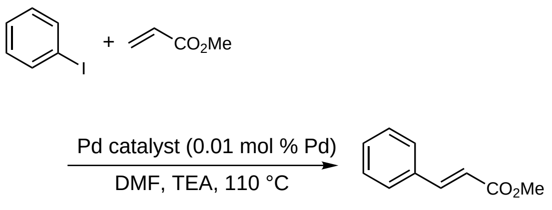
[a] Isolated yields.
[b] Lit. 210 °C.[25a]
[c] Lit.150 – 152 °C.[25a]
[d] Lit. 156 – 160 °C.[25b,26]



Scheme 3.

dated oxime as we initially assumed.[22] Instead, it was obtained a mixture of compounds the structures of which are now under investigation in our laboratory. Preliminary results have shown that carbopalladation did not take place in this case. The fact that fluorenone oxime was not cyclopalladated {not even under ligand-exchange conditions[25d,28] with $[Pd(dmba)Cl]_2$, (dmba = *N*,*N*-dimethylbenzylamine)}, could be a consequence of the rigidity conferred to the system by the two linked aromatic rings, which was not the situation in similar di- and polycyclic systems that have been easily palladated and where only one aromatic ring was present in the molecule.[29]

Heck Coupling of Aryl Halides with Olefins



Scheme 4.

The arylation of olefins with aryl halides was first evaluated with palladium complexes **16**–**18** in order to study their catalytic activity. We chose as a model reaction the coupling between methyl acrylate and phenyl iodide (PhI)[30] in DMF at 110 °C, in the presence of triethylamine (TEA) as base and with a catalyst loading of 10^{-2} mol % in Pd (Scheme 4, Table 2). The reaction provided very similar results and quantitative conversions under air for nearly all the dimeric complexes with reaction periods within 1.5 h (for the 4,4′-dichlorobenzophenone oxime derivative **16d**) and 24 h for monometallated dioxime complex **16e**. Complexes **16a**, **b**, and **d**, gave similar conversions and rates, however, the reaction with the *p*-methoxy-substituted benzophenone complex **16c** was rather slower under the same reaction conditions (compare entries 1, 2, 3, and 4, Table 2). This result clearly shows that, with respect to catalyst efficiency, complexes containing electron-donating groups in the aryl ring are inferior to precursors substituted with neutral or electron-withdrawing groups. A catalyst system prepared *in situ* from Li_2PdCl_4 (0.01 mol % of Pd) and 4,4′-dichlorobenzophenone oxime (0.01 mol %) in the presence of base (excess of K_2CO_3), was tested as well (Table 2, entry 8). In this case, the yield was significantly lower (62% after 6 h) than that obtained from the straight use of **16d** (full conversion after 1.5 h). This result is obvious as the formation of the complex takes longer reaction periods and Li_2PdCl_4 itself catalyzes the reaction with lower rates (90% yield after 3.5 h) (Table 2, entry 9).

The optimum reaction conditions for the palladacycle catalysts were studied for the coupling reaction of phenyl iodide and methyl acrylate in the presence of

Table 2. Heck coupling: catalyst study.

Entry	Catalyst	t [h]	Yield [%][a],[b]	TON[c]	TOF [h^{-1}][d]
1	**16a**	2	98	9800	4900
2	**16b**	2	98	9800	4900
3	**16c**	6	85	8500	1417
4	**16d**	1.5	> 99	10000	6667
5	**16e**	24	93	9300	388
6	**17**	4	98	9800	2450
7	**18**	6	94	9400	1567
8	**16d**[e]	6	62	6200	1033
9	Li_2PdCl_4	3.5	90	9000	2571

[a] Determined by GLC, based on PhI using decane as internal standard.
[b] Reaction conditions: PhI (2 mmol), methyl acrylate (2.4 mmol), TEA (2.8 mmol), catalyst, DMF (4 mL).
[c] TON = turnover number (mol product mol Pd^{-1}).
[d] TOF = turnover frequency (TON h^{-1}).
[e] **16d** was generated *in situ* in the reaction medium.

Scheme 5.

catalysts **16b** or **16d** (Scheme 5, Table 3).[30] The reaction afforded quantitative conversions with either DMF or NMP as solvents at 110 °C under air[31] using 10^{-2} mol % of Pd in 2 or 1.5 h, respectively (Table 3, entries 1 and 2). When using other different solvents, CH_3CN, dioxane, and DME, the reaction became slower, while experiments run in THF, DMSO, and toluene gave very low conversions. During the course of our studies, we examined several different bases: TEA, K_2CO_3, and CsF can be used, the reaction being faster with TEA (Table 3, entries 1, 9 and 10). At 110 °C, reducing the catalyst loading to 10^{-3} mol % Pd led to longer reaction times, but did not influence the reaction conversion (Table 3, compare entries 1 and 11). When the catalyst loading was brought down to 10^{-4} mol % of Pd (Table 3, entry 13), the activity of the complex dropped significantly to give a 35% yield of methyl cinnamate after two days. However, this problem could be overcome by just increasing the reaction temperature to 160 °C (bath temperature). Under these conditions, the reaction was completed within 9 h (Table 3, entry 14) and it was possible to decrease the amount of Pd down to 10^{-6} mol % with reproducible results for methyl and *n*-butyl acrylate (Table 3, entries 15 and 16). In both cases impressive TON numbers were obtained (10^8) with very good isolated yields. These results are the average of 3 runs (the reactions were run under similar conditions in a Carousel Reaction Station™, see Experimental Section). In the case of employing lower catalyst loading such us 10^{-8} mol % of Pd (Table 3, entry 17), conversions ranging from 80 to 98% could be reached (average of 6 runs) after 3 d affording turnover numbers of 10^{10} and turnover frequencies of 1.4×10^8 h^{-1} which is, to the best of our knowledge, the highest catalytic activity of all Heck reactions reported to date.[32] As mentioned above, the isolated yields of *n*-butyl cinnamate after flash chromatography were in complete agreement with the conversions. Even under these very low catalyst loading limits, the reactions can be carried out in air without any previous purifications of phenyl iodide, the olefin, or the solvent. However, it is very important to eliminate possible traces of catalyst from the reaction vessel and the stirring bar in order to avoid what Dupont has called “reaction vessel catalytic activity”.[33] Then, under these very low catalyst loadings, the reaction vessels and the stirring bar were always washed with concentrated nitric acid prior to run a new catalytic cycle with them.[34]

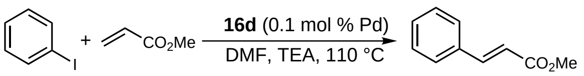
The pronounced thermal stability of palladacycles **16** was demonstrated by the absence of Pd-black precipitation after heating catalyst **16d** in a DMF solution for 5 h. Only trace amounts were found after longer reactions periods. Additionally, no deactivation of the catalyst was observed in subsequent catalytic runs when coupling phenyl iodide and methyl acrylate under typical conditions (**16d**, 0.1 mol % of Pd), and GLC analysis of 4 cycles yielded a constant rate of conversion

Table 3. Heck coupling: reaction conditions study.

Entry	**16** [% mol Pd]	R	Solvent	Base	T [°C]	t [h]	Yield [%][a],[b]	TON	TOF [h^{-1}]
1	**16b** (10^{-2})	Me	NMP	TEA	110	1.5	99 (92)	9900	6600
2	**16b** (10^{-2})	Me	DMF	TEA	110	2	98	9800	4900
3	**16b** (10^{-2})	Me	CH_3CN	TEA	110	5	58	5800	1160
4	**16b** (10^{-2})	Me	THF	TEA	110	7	23	2300	329
5	**16b** (10^{-2})	Me	DMSO	TEA	110	1	2	200	200
6	**16b** (10^{-2})	Me	dioxane	TEA	110	4.5	72	7200	1600
7	**16b** (10^{-2})	Me	toluene	TEA	110	4.5	31	3100	689
8	**16b** (10^{-2})	Me	DME	TEA	110	4.5	52	5200	1156
9	**16b** (10^{-2})	Me	NMP	K_2CO_3	110	4.5	97	9700	2156
10	**16b** (10^{-2})	Me	NMP	CsF	110	3.5	> 99	10000	2857
11	**16b** (10^{-3})	Me	NMP	TEA	110	12	> 99	10^5	8300
12	**16d** (10^{-2})	Me	DMF	TEA	110	1.5	> 99	10000	6667
13	**16d** (10^{-4})	Me	DMF	TEA	110	48	35	3.5×10^5	73000
14	**16d** (10^{-4})	Me	DMF	TEA	160	9	> 99	10^6	110000
15	**16d** (10^{-6})	Me	DMF	TEA	160	10	> 99(94)	10^8	10^7
16	**16d** (10^{-6})	*n*-Bu	DMF	TEA	160	24	> 99(98)	10^8	4.2×10^6
17	**16d** (10^{-8})	*n*-Bu	DMF	TEA	160	72	> 99(98)	10^{10}	1.4×10^8

[a] Determined by GLC, based on PhI using decane as internal standard. In parenthesis isolated yield after flash chromatography.

[b] Reaction conditions: PhI (2 mmol), alkyl acrylate (2.4 mmol), base (2.8 mmol), **16**, solvent (4 mL).



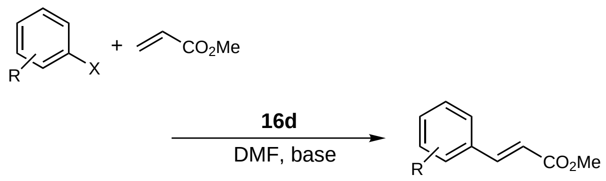
First cycle: 99%, 1.2 h
Second cycle: 97%, 1.5 h
Third cycle: 98%, 2 h
Fourth cycle: 96%, 2 h

Scheme 6.

of phenyl iodide after adding fresh reagents to the solution (Scheme 6). After the coupling, the reaction mixture usually exhibited the typical yellow-orange colour of palladium in the divalent oxidation state or colourless when very low catalyst concentrations were used. In fact, only Pd(II) could be detected by XPS experiments in the crude reaction mixture after the coupling was finished once the DMF and the methyl cinnamate were evaporated under high vacuum conditions.

It is interesting to note that the catalyst in the first run exhibited an induction period of about 20 min, signifying that the catalytically active species, probably Pd(0) nanoparticles,[4] was formed during the course of the reaction.[35,36] This induction stage disappeared in successive runs and when the catalyst, previously heated in DMF, was used for the first run of the Heck coupling. In this latter case higher conversions in shorter reaction times were always obtained if compared when no “pre–activation” of the oxime-derived palladacycle was carried out (55% conversion *versus* no conversion after 20 min and 99% conversion *versus* 35% conversion after 35 min). The activation of the catalyst only took place in this particular case. No activation was observed when **16d** was previously heated for 3.5 h with phenyl iodide, TEA, or methyl acrylate in DMF, where lower conversions were always obtained when compared with the standard reaction. A heavy precipitation of Pd black was observed when complex **16d** was heated in the presence of methyl acrylate probably due to Pd-C bond cleavage with C-C bond-forming reductive elimination.[6a]

We next investigated the reaction of various aryl halides with methyl acrylate (Scheme 7, Table 4). In the case of substituted aryl iodides, C-C coupling in the presence of TEA and catalytic amounts of **16d** led quantitatively to the corresponding methyl cinnamates. Table 4 entries 1–5 summarize the results of the catalyzed reactions showing high reactivity for sterically



Scheme 7.

Table 4. Heck coupling of aryl halides with methyl acrylate catalyzed by **16d**.

Entry	**16d** [mol % Pd]	R	X	Base	T [°C]	t [h]	Yield [%][a],[b]	TON
1	0.01	1-iodonaphthalene		TEA	110	24	> 99	10000
2	0.01	*o*-CH_3	I	TEA	110	3	> 99 (99)	10000
3	0.01	*p*-CH_3O	I	TEA	110	5	94	9400
4	0.01	*p*-CH_3CO	I	TEA	110	6	97	9700
5	0.01	*p*-Cl	I	TEA	110	5	> 99	10000
6	0.5	*p*-CH_3CO	Br	K_2CO_3[c]	130	5.5	90	180
7	0.5	*p*-NO_2	Br	K_2CO_3[c]	130	2	> 99	200
8	2	*p*-NO_2	Br	K_2CO_3[c]	130	2	58	29
9	0.5	H	Br	K_2CO_3[c]	130	24	49	98
10	0.5	1-bromonaphthalene		K_2CO_3[c]	130	4	91	182
11	0.5	*p*-CH_3	Br	K_2CO_3[c]	130	6	54	108
12	0.5	*p*-Ph	Br	K_2CO_3[c]	130	24	80	160
13	0.5	*o*-CH_3	Br	K_2CO_3[c]	130	24	24	49
14	0.5	*p*-CH_3O	Br	K_2CO_3[c]	130	9	57	113
15	0.5	*o*-Br	Br	K_2CO_3[c]	130	5	92	185
16	0.5	3,5-dibromo	Br	K_2CO_3[c]	130	3	100	200
17	0.5[d]	*p*-NO_2	Cl	K_2CO_3[c]	130	5	77 (65)	154
18	0.1[d]	*p*-NO_2	Cl	K_2CO_3[c]	160	4.5	92	920
19	0.2	*p*-OMe	Cl	Cs_2CO_3 [e]	160	24	23	115

[a] Determined by GLC, based on ArX using decane as internal standard. In parenthesis, isolated yield after flash chromatography.

[b] Reaction conditions: ArX (2 mmol), methyl acrylate (2.4 mmol), base (2.8 mmol), DMF (4 mL), **16d**.

[c] The reaction was performed in the presence of TBAB (20 mol %).

[d] *n*-Butyl acrylate was used as the olefin.

[e] The reaction was performed in 1,4-dioxane and using LiBr (20 mol %) and *n*-butyl acrylate as the olefin.

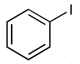
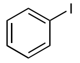
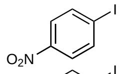
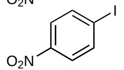
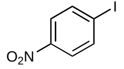
hindered *ortho*-substituted aryl iodides (entry 2). TOF numbers generally ranged from 415 to 6700. Less reactive electron-rich aryl iodides (Table 4, entries 2 and 3), did not require either higher catalyst concentrations or longer reaction times.

The catalytic activity with aryl bromides[37] depends on the substitution of the aryl moiety (Table 4, entries 6–16). When the reaction was performed under Jeffery's conditions,[38] electron-withdrawing groups on the aryl ring such as *p*-NO_2 and *p*-CH_3CO increased the reaction rate (Table 4, entries 6 and 7). When increasing the catalyst loading from 0.5 to 2 mol % in the coupling of *p*-bromonitrobenzene with methyl acrylate, the reaction rate diminished noticeably probably due to palladium metal aggregation (58% conversion after 2 h, 85% after 6 h). The coupling of 1-bromonaphthalene and methyl acrylate was finished in 4 h affording the corresponding product in an excellent 91% yield. On the contrary, bromobenzene, a relatively inactive halide, gave a 49% yield of (*E*)-methyl cinnamate after 24 h. Bromobenzenes substituted with electron-donating groups (Table 4, entries 11–14) required longer reaction times, especially when increasing the steric hindrance via *ortho*-substitution (Table 4, entry 13). Excellent yields were obtained when polybromobenzenes such us 1,2-dibromobenzene and 1,3,5-tribromobenzene reacted with an excess of olefin affording the corresponding aromatic di- and triacrylic methyl esters.[39] *ortho*-Diethenylarenes have been used in the synthesis of annulenes[40] and furans[41] as well as for the preparation of enantiomerically pure *cis*-pentacin derivatives[42] and antitumor antibiotics.[43] On the other hand, 1,3,5-triethenylarenes could be used as a three-directional core for a divergent dendrimer synthesis[44] (Scheme 8 and Table 4, entries 15 and 16).

We were pleased to observe that aryl chlorides[37] can also be used (Table 4, entries 17–19). For example, the coupling reaction of *p*-nitrochlorobenzene with methyl acrylate mediated by **16d** under Jeffery's conditions gave the desired cinnamate in a 65% yield (entry 17). When lower catalyst loadings were used (0.1 mol % of Pd, Table 4, entry 18) it was necessary to increase the reaction temperature to 160 °C for similar reaction times, employing, in this case, *n*-butyl acrylate as the olefin to give the corresponding cinnamate in a 92% yield. In the case of using *p*-chloroacetophenone, Michael addition to the alkene was a competing side reaction which predominated at these high temperatures. When a deactivated aryl chloride such us *p*-chloroanisole was coupled with *n*-butyl acrylate, TBAB was replaced by LiBr as cocatalyst and the reaction was carried out in the presence of Cs_2CO_3 and dioxane at 160 °C to give the substituted product in a low yield (23%).

In order to study the effect of the olefin in the Heck coupling, the reaction of aryl halides with styrene, *p*-methoxystyrene, *p*-chlorostyrene, acrylonitrile, 2,3-dihydrofuran and ethyl vinyl ether, was investigated in the presence of palladacycles **16.** The results are summarized in Tables 5–7. In the case of aryl iodides (Scheme 9, Table 5), styrene gave very good conversions, with non-activated and activated substrates employing catalyst loadings between 0.1 and 0.01 mol % of Pd. With phenyl iodide (Table 5, entry 2) it was possible to reduce the catalyst loading to 10^{-2} mol % of Pd to produce a mixture of α- and β-arylated products (α/β = 1/7) in 87% total yield (TON = 8700, TOF = 100 h^{-1}). The reaction

Table 5. Heck coupling of aryl iodides with olefins catalyzed by **16**.

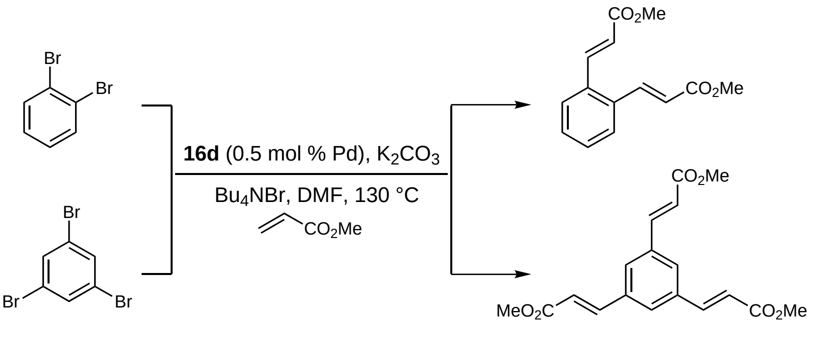
Entry	Aryl Iodide	R	**16**[a] [mol % Pd]	t [h]	Yield[b] [%]	TON
1		Ph	**16b** (0.1)	4	98[c]	980
2		Ph	**16b** (0.01)	29	87[c]	8700
3		*p*-$MeOC_6H_4$	**16d** (0.1)	6	40	400
4		*p*-ClC_6H_4	**16d** (0.1)	6	35	350
5		CN	**16d** (0.1)	9	53[d]	530

[a] Reaction conditions: ArI (2 mmol), alkene (2.4 mmol), TEA (2.8 mmol), **16**, DMF (4 mL), 110 °C (bath temperature).

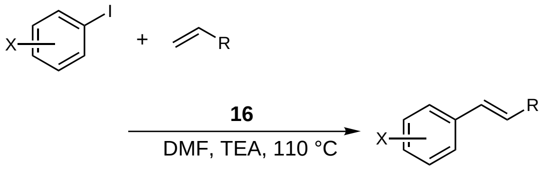
[b] Determined by GLC, based on ArI using decane as internal standard.

[c] α-Arylation product was also detected by GLC and ^{1}H NMR analysis of the crude reaction mixture in a 11% yield.

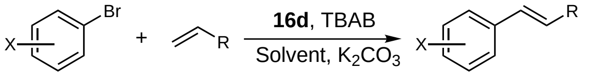
[d] *E*/*Z* = 6/1, determined by ^{1}H NMR of the crude reaction mixture.



Scheme 8.



Scheme 9.



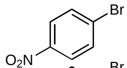
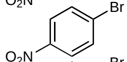
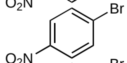
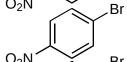
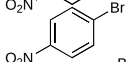
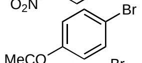
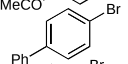
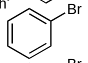
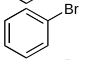
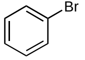
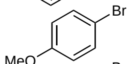
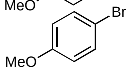
Scheme 10.

of *p*-iodonitrobenzene with other olefins led to the resultant coupled products in moderate to good yields (Table 5, entries 3–5).

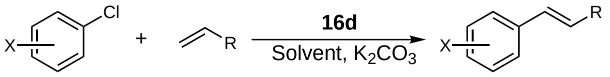
The reaction of activated aryl bromides, such as *p*-bromoacetophenone and *p*-bromonitrobenzene with different olefins under PTC conditions, consistently resulted in reasonable yields of 40–99% with 0.25 mol % of **16d** (Scheme 10, Table 6, entries 1–6). The coupling of 4-substituted styrenes with *p*-bromonitrobenzene (Table 6, entries 1–3), led to the corresponding stilbenes with very good yields in all cases, providing evidence that the efficiency of the catalyst in this particular case is not so sensible towards electronic factors. The reaction of *p*-bromonitrobenzene with enol ethers, such us ethyl vinyl ether, showed a strong preference for the β-arylation as reported by Herrmann et al.[7a] In fact, no α-arylation product was detected by GLC analysis (Table 6, entry 5). In the case of acrylonitrile, a mixture of (*E*)- and (*Z*)-4-nitrocinnamonitrile in 74% yield (58/14) (Table 6, entry 4) was obtained. The reaction with 2,3-dihydrofuran afforded a mixture of regioisomers in a 74/7 ratio (Table 6, entry 6). Bromobenzene, a relatively deactivated halide, gave 92% isolated yield of *trans*-stilbene after 2 h using only 0.2 mol % of Pd at 160 °C (Table 6, entry 8). The reaction also worked (Table 6, entry 9) in the absence of TBAB, affording nearly the same yield but with lower turnover rates (3.5 h) and with a higher amount of α-arylated product (1,1-diphenylethene, 10%). To test the activity of the palladacycle **16d** with bromobenzene, the reaction was performed using only 10^{-3} mol % of Pd (Table 6, entry 10), achieving at 160 °C in NMP as solvent, very good activity (TON = 88000, TOF = 3667 h^{-1}). Prompted by this very promising result, the activity of the oxime-derived catalyst was tested with deactivated substrates such as *p*-bromoanisole which, after only 16 h and using 10^{-3} mol % of Pd under air, gave the corresponding stilbene with excellent conversions (97% conversion, 85% yield) and with record figures with respect to catalyst activity (TON = 97000, TOF = 6063 h^{-1}).[45]

With regard to aryl chlorides (Scheme 11, Table 7), *p*-chloronitrobenzene, an activated substrate, afforded (*E*)-4-nitrostilbene in high yield (93% conversion, 70% isolated yield, TON = 186, Table 7, entry 1). As illustrated in entries 2–4, Heck couplings of *p*-chloroacetophenone with styrene proceeded with low conversions under standard conditions (0.5 mol % of Pd, 130 °C) and no progress was made when a higher concentration of TBAB (50 mol %) was used (entry 3), probably due to the blocking of free coordination sites of low-ligated palladium(0) complexes by the excess of halide concentration.[46] Once more, just by increasing the reaction temperature to 160 °C and in the presence of 20 mol % of TBAB, the desired (*E*)-4-acetylstilbene was obtained in a very good yield in only 2 h. Only in the case of the Heck coupling with *p*-chloronitrobenzene did the elec-

Table 6. Heck coupling of aryl bromides with olefins catalyzed by **16d**.

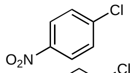
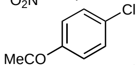
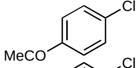
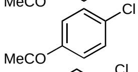
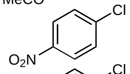
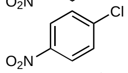
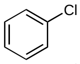
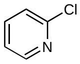
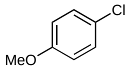
Entry	Aryl Bromide	R	[mol % Pd][a]	T [°C]	t [h]	Yield [%][b]	TON
1		Ph	0.5	130	2	87(65)	174
2		*p*-MeOC$_6$H$_4$	0.5	130	4	>99(99)[c]	200
3		*p*-ClC$_6$H$_4$	0.5	130	4	>99(97)	200
4		CN	0.5	130	4	72[d]	144
5		OEt	0.5	130	5	40[e],[f]	80
6		-[g]	0.5	130	2	83[h]	166
7		Ph	0.5	130	6	83(45)	166
8		Ph	0.2[i]	160	2	>99(98)[j]	500
9		Ph	0.2[i],[k]	160	3.5	96[j]	480
10		Ph	0.001[i]	160	24	88[j]	88000
11		Ph	0.2[i]	160	2	>99(78)[l]	500
12		Ph	0.001[i]	160	16	97(85)[l]	97000

[a] Reaction conditions: ArBr (2 mmol), alkene (2.4 mmol), K_2CO_3 (2.8 mmol), TBAB (20 mol %), **16d**, DMF (4 mL).
[b] Determined by GLC, based on ArBr using decane as internal standard. In parenthesis, isolated yield after flash chromatography.
[c] α-Arylation product was obtained in a 3% yield, determined by GLC analysis of the crude reaction mixture.
[d] E/Z = 4/1, determined by ^1H NMR of the crude reaction mixture.
[e] E/Z = 5/3, determined by ^1H NMR of the crude reaction mixture.
[f] Significant amounts of bis-*p*-nitrophenyl ether were also obtained.
[g] 2,3-Dihydrofuran.
[h] 10/1 Mixture of regioisomers: 5-(4-acetophenyl)-2,3-dihydrofuran (74%) and 2-(4-acetophenyl)-2,3-dihydrofuran (7%).
[i] The reaction was carried out in NMP (4 mL).
[j] α-Arylation product was detected by GLC and ^1H NMR analysis of the crude reaction mixture in ca. 6% yield.
[k] The reaction was carried out in the absence of TBAB.
[l] E/Z = 9/1, determined by GLC analysis of the crude reaction mixture.



Scheme 11.

Table 7. Heck coupling of aryl chlorides with styrenes catalyzed by **16d**.

Entry	Aryl Chloride	R	[mol% Pd][a]	T [°C]	t [h]	Yield[b] [%]	TON
1		Ph	0.5	130	8	93(70)	186
2		Ph	0.5	130	4	40	80
3		Ph	0.5	130	4	35[c]	70
4		Ph	0.5	160	2	100	200
5		p-MeOC$_6$H$_4$	0.5	160	6	90(80)[d]	180
6		p-ClC$_6$H$_4$	0.5	160	4	>99(95)	200
7		Ph	0.5[e]	160	24	60[f]	120
8		Ph	0.5[e]	160	30	70[g]	140
9		Ph	0.2[e],[h]	160	24	22	110

[a] Reaction conditions: ArCl (2 mmol), alkene (2.4 mmol), K$_2$CO$_3$ (2.8 mmol), TBAB (20 mol %), DMF (4 mL).

[b] Determined by GLC, based on ArCl using decane as internal standard. In parenthesis isolated yield after flash chromatography.

[c] 50 mol % of TBAB was used.

[d] α-Arylation product was also detected by GLC and ^{1}H NMR analysis of the crude reaction mixture in a 8% yield.

[e] The reaction was performed in NMP.

[f] α-Arylation product was also detected by GLC and ^{1}H NMR analysis of the crude reaction mixture in a 6% yield.

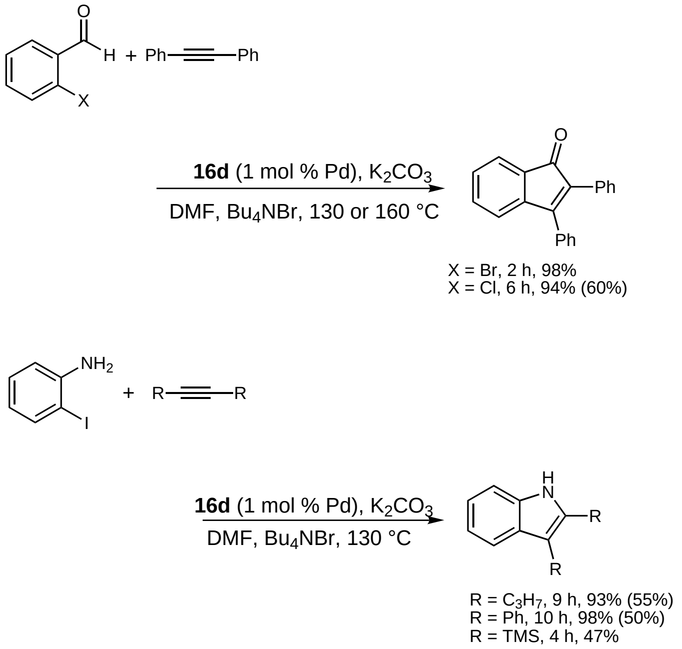
[g] α-Arylation product was also detected by GLC and ^{1}H NMR analysis of the crude reaction mixture in a 13% yield.

[h] LiBr (20 mol %) was used instead of TBAB.

tronic nature of the olefin come up as an important feature. p-Chlorostyrene showed higher reaction rate and better regioselectivity than p-methoxystyrene (Table 7, entries 5 and 6). Non-activated aryl chlorides, such as chlorobenzene and 2-chloropyridine took longer reaction times in the Heck coupling reaction with styrene but still the substitution products were obtained in good yields (60% and 70%, respectively). In the case of deactivated aryl chlorides (p-chloroanisole), a dramatic salt effect appeared as TBAB (no conversion after 48 h) had to be replaced by LiBr to afford the corresponding stilbene in 22% yield, showing that small changes in the co-catalyst really improve the catalyst productivity.

Annulation Reactions of Internal Alkynes Catalyzed by Palladacycles 16

The synthesis of 2,3-disubstituted indenones[47] and indoles[48] via annulation of internal alkynes[49] with 2-bromobenzaldehyde, 2-chlorobenzaldehyde, and 2-iodoaniline, respectively, was achieved with 0.5 mol % of palladacycle **16d** with yields ranging from 47 to 98% (Scheme 12). 2-Bromobenzaldehyde and 2-chlorobenzaldehyde reacted with tolane to produce 2,3-diphenylindenone in a 98 and 94% conversion, respectively. However 2-iodoaniline reacted with both hindered and unhindered alkyl-, silyl-, and aryl-substituted alkynes such as 4-octyne, bis(trimethylsilyl)acetylene, and tolane with the conversions showed in Scheme 12.[50] This annulation chemistry clearly demonstrates the versatility of oxime-derived palladacycles, as indenones and indoles are important features of a variety of natural and medicinal products.



Scheme 12.

Conclusion

In conclusion, oxime-derived palladacycles represent very efficient catalyst precursors for the Heck olefination of haloarenes. Extraordinary turnover numbers and rates have been obtained *under aerobic conditions* for aryl iodides (TON up to 10^{10} and TOF up to 1.4×10^8 h^{-1}) and deactivated aryl bromides (TON up to 97000, TOF up to 6063 h^{-1}). Aryl chlorides presented turnover numbers up to 920 in the Heck coupling with olefins, showing an important salt effect in the reaction performance, in the case of deactivated substrates. Moreover, we have shown these systems as competent catalysts for the palladium-catalyzed annulation of internal alkynes by o-iodoaniline, o-bromo-, and o-chlorobenzaldehyde to afford indoles and indenones in good to excellent yields. These catalysts are thermally stable complexes not sensitive to air or moisture and can be synthesized from readily cheap and available starting materials using a straightforward procedure. Their easy synthetic accessibility and structural versatility make these complexes very promising catalysts and further studies in their applicability in other organic transformations are currently under investigation.

Experimental Section

General

The reagents and solvents were obtained from commercial sources and were generally used without further purification. Gas chromatographic analyses were performed on an HP-5890 instrument equipped with a WCOT HP-1 fused silica capillary column. ^{1}H NMR spectra were recorded on Bruker AC-300 MHz (300 MHz) and Bruker Avance (500 MHz). Chemical shifts are reported in ppm using either tetramethylsilane (TMS, 0.00 ppm) or DMSO as internal standards. ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$, DMSO-d_6 or DMF-d_7 as the internal reference. The catalysts were weighed up in an electronic microscale (Sartorius, XM1000P) with precision of 1 μg. IR data were collected on a Nicolet Impact 400D of FT. The XPS spectra have been obtained with a VG-Microtech Multilab electron spectrometer, by using the Mg Kα (1253.6 eV) radiation of twin anode in the constant analyser energy mode with pass energy of 50 eV. Pressure of the analysis chamber was maintained at $5 \cdot 10^{-10}$ mB. The binding energy and the Auger kinetic energy scale were regulated by setting the C1s transition at 284.6 eV. The accuracy of BE and KE values was ± 0.2 and ± 0.3 eV, respectively. The BE and KE values were obtained by using the Peak-fit Program implemented in the control software of the spectrometer. The reactions were set up in parallel with the aid of an RR98030 12 place Carousel Reaction Station™ equipped with gas tight threaded caps with valve, cooling reflux head system and digital temperature controller from Radleys Discovery Technologies.

Synthesis of Palladacycles 16a – 16d and 17 – 18

To a solution of Li_2PdCl_4 (2.62 g, 10 mmol) in methanol (20 mL), a methanolic solution (10 mL) of the corresponding oxime (10 mmol) and sodium acetate (0.82 g, 10 mmol) was added. Then, the solution was stirred for 2 to 3 d at room temperature, the mixture was filtered and after adding water (10 mL), the corresponding cyclopalladated complexes precipitated. The different catalysts **16** were obtained with yields between 60 – 98%. Yields and physical data are given in Table 1, spectral data follow:

Catalyst 16a: IR (KBr): $\nu = 3430$ (OH), 1638 (C = N) cm^{-1}; ^{1}H NMR (DMF-d_7): $\delta = 2.31$ (s, 6H, 2× $CH_3C = N$), 6.94 – 6.99 (m, 2H, ArH), 7.04 – 7.09 (m, 2H, ArH), 7.23 – 7.26 (m, 2H ArH), 7.62 – 7.64 (m, 2H, ArH), 10.30 (m, 2H, NOH); ^{13}C NMR (DMF-d_7): $\delta = 11.05$, 124.8, 126.2, 128.4, 135.6, 143.4, 150.6, 167.9.

Catalyst 16b: IR (KBr): $\nu = 3373$ (OH), 1645 (C = N) cm^{-1}; ^{1}H NMR (DMF-d_7): $\delta = 6.73$ (m, 2H, ArH), 7.00 (m, 4H, ArH), 7.59 (m, 10H, 2× PhH), 7.76 (m, 2H, ArH), 10.47 (m, 2H, NOH); ^{13}C NMR (DMF-d_7): $\delta_C = 124.8$, 127.9, 128.4, 129.2, 129.5, 130.2, 130.6, 136.1, 143.7, 151.1, 167.6.

Catalyst 16c: IR (KBr): $\nu = 3389$ (OH), 1607 (C = N), 1253 (C-O) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 3.72$ (s, 6H, 2× OCH_3), 3.83 (s, 6H, 2× OCH_3), 6.73 (m, 4H, ArH), 7.09-7.44 (m with 2d, $J = 8.6$ Hz, 10H, ArH), 9.88, 10.30 (2m, 2H, NOH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 55.2$, 55.3, 110.5, 113.3, 113.5, 118.8, 120.7, 128.8, 130.9, 131.2, 134.3, 152.6, 158.3, 160.8, 165.8.

Catalyst 16d: IR (KBr): $\nu = 3691 – 3100$ (OH) cm^{-1}; ^{1}H NMR (DMF-d_7): $\delta = 6.76$ (d, 2H, $J = 7.93$ Hz, ArH), 7.11 (dd, 2H, $J = 7.93$, 1.83 Hz, ArH), 7.64 – 7.71 (m, 8H, ArH), 7.78 (m, 2H, ArH), 10.83 – 10.86 (m, 2H, NOH); ^{13}C NMR (DMF-d_7): $\delta = 124.9$, 128.8, 129.0, 129.5 131.5, 133.0, 135.4, 136.0, 142.2, 152.0, 166.6.

Catalyst 17: IR (KBr): $\nu = 3080 – 3590$ (OH), 1655 (C = N) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta_H = 1.17$ (s, 12H, 4× CH_3C), 1.91 (s, 6H, 2× $CH_3C = N$), 2.36 (s, 4H, 2× CH_2 Pd), 9.82 (s, 2H, 2× NOH); ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 12.1$, 27.6, 48.2, 48.7, 178.8.

Catalyst 18: IR (KBr): $\nu = 3404$ (OH), 1622 (C = N) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.19$ (s, 6H, 2× CH_3), 4.14-4.29 (m, 12H, 2× ArH), 4.58 (s, 2H, 2× ArH), 4.78 (s, 2H, ArH), 9.41 (s, 2H, 2× NOH).

Synthesis of Palladacycle 16e

A solution of $PdCl_2(PhCN)_2$ (188 mg, 0.49 mmol) and the oxime (94 mg, 0.49 mmol) in acetonitrile (20 mL) was refluxed at 85 °C for 4 h. Then, the precipitate was filtered and dried (15 mm Hg) to afford catalyst **16e**; yield: 40%. IR (KBr): $\nu =$ 3454 (OH), 1615, 1604 (C = N) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 2.27$, 2.30 (2s, 12H, 4× CH_3), 7.03 (s, 2H, ArH), 7.24 (m, 4H, ArH), 10.15 (s, 2H, 2× NOH), 11.84 (s, 2H, 2× NOH); ^{13}C NMR (DMSO-d_6): $\delta = 11.2$, 22.2, 118.7, 123.3, 125.9, 130.8, 136.7, 143.0, 165.6, 166.8.

Reduction of Complexes 16 with Sodium Cyanoborodeuteride

To a mixture of the complex to be reduced (0.125 mmol) in THF (2.5 mL) and MeOH (1.25 mL), sodium cyanoborodeuteride (0.25 mmol, 168 mg) was added portionwise at 0 °C and the mixture was stirred for 1 h allowing to warm to room temperature. The black precipitate was filtered off, the solvents were evaporated (15 mm Hg) and the residue hydrolyzed with water, extracted with dichloromethane, the organic layer dried (Na_2SO_4), and evaporated (15 mm Hg). The different deuterated oximes were obtained with yields between 90 – 99%.

Deuterated oxime 20a: R_f: 0.63 (hexane/EtOAc, 3/2); mp 52 – 53 °C; IR (KBr): $\nu = 3239$ (OH), 1645 (C = N) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 2.14$ (s, 3H, CH_3), 7.36 – 7.65 (2m, 4H, ArH), 11.17 (s, 1H, NOH); ^{13}C NMR (DMSO-d_6): $\delta = 11.5$, 125.5, 128.2, 128.3, 128.6, 136.9, 137.0 and 152.9; MS: m/z (rel. int.) = 136 (M^+, 39), 135 (49), 107 (13), 106 (12), 104 (20), 103 (21), 95 (18), 94 (17), 79 (29), 78 (100), 77 (95), 76 (18), 67 (16), 66 (25), 65 (13), 63 (11), 52 (43), 51 (82), 50 (42), 42 (26), 40 (22).

Deuterated oxime 20b: R_f: 0.74 (hexane/EtOAc, 3/2); mp 143 – 144 °C; IR (KBr): $\nu = 3243$ (OH), 1660 (C = N) cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta = 7.87 – 8.04$ (2m, 9H, ArH), 9.35 – 9.52 (m, 1H, NOH); ^{13}C NMR (DMSO-d_6): $\delta = 126.9$, 127.0, 128.1, 128.2, 128.3, 128.4, 128.8, 128.9, 135.5, 136.65, 136.74, 155.1; MS: *m/z* (rel. int.) = 198 (M^+, 44), 197 (M^+-1, 28), 181 (45), 180 (28), 166 (14), 165 (12), 104 (11), 94 (12), 90 (14), 83 (20), 78 (43), 77 (100), 52 (26), 51 (79), 50 (29).

Deuterated oxime 20c: R_f: 0.46 (hexane/EtOAc, 3/2); mp 134–136 °C; IR (KBr): $\nu = 3227$ (OH), 1609 (C=N), 1252 (C-O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.82$, 3.87 (2s, 6H, 2× OCH_3), 6.84–6.87 (m, 2H, ArH), 6.99 (d, $J = 8.6$ Hz, 2H, ArH), 7.40–7.44 (m, 3H, ArH), 11.00 (s, 1H, NOH); ^{13}C NMR ($CDCl_3$): $\delta =$ 55.2, 55.3, 113.5, 113.6, 113.7, 124.9, 129.1, 129.2, 129.4, 131.1, 157.0, 160.0, 160.6; MS: *m/z* (rel. int.) = 243 (M^+-1, 26), 242 (11), 212 (13), 136 (67), 135 (100), 107 (12), 93 (11), 92 (16), 78 (19), 77 (33), 64 (15).

Deuterated oxime 20d: R_f: 0.68 (hexane/EtOAc, 3/2); mp 136–137 °C; IR (KBr): $\nu = 3617-3093$ (OH), 1630 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): $\delta = 7.30-7.46$ (m, 5H, ArH), 7.53 (d, $J = 8.6$ Hz, 2H, ArH), 11.58 (s, 1H, NOH); ^{13}C NMR (DMSO-d_6): $\delta = 128.3$, 128.4, 128.5, 128.59, 128.60, 130.9, 131.7, 133.3, 133.7, 135.1, 135.2, 153.2; MS: *m/z* (rel. int.) = 268 (M^++2, 28), 266 (M^+, 49), 251 (25), 250 (25), 249 (35), 248 (21), 215 (18), 154 (24), 153 (39), 139 (17), 138 (20), 114 (15), 113 (27), 112 (46), 111 (58), 100 (19), 82 (34), 75 (100), 52 (15), 51 (46), 54 (59), 40 (17).

Deuterated oxime 20e: R_f: 0.53 (EtOAc); IR (KBr): $\nu = 3299$ (OH), 1663, 1608 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): $\delta =$ 7.27–7.29 (m, 2H, ArH), 7.55–7.57 (m, 1H, ArH), 7.90 [s, 0.4H, ArH (partially deuterated)], 9.96 (s, 1H, NOH), 11.18 (s, 1H, NOH); MS: *m/z* (rel. int.) = 193 (M^+, 22%), 192 (M^+-1, 14), 151 (19), 150 (14), 134 (18), 133 (15), 119 (14), 109 (17), 93 (14), 92 (16), 81 (14), 66 (16), 65 (14), 64 (11), 44 (31), 43 (100).

Deuterated oxime 22: R_f: 0.68 (hexane/EtOAc, 3/2); IR (KBr): $\nu = 3631-3174$ (OH), 1647 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): $\delta = 2.04$ (s, 3H, CH_3CNOH), 4.16 (s, 5H, ArH), 4.30, 4.51 (2s, 3H, ArH), 10.57 (s, 1H, NOH); ^{13}C NMR (DMSO-d_6): $\delta = 12.6$, 66.08, 66.11, 68.9, 69.0, 82.6, 82.7, 152.9; MS: *m/z* (rel. int.) = 244 (M^+, 100), 243 (20), 228 (10), 138 (24), 130 (11), 129 (10), 121 (29), 106 (12), 105 (12), 95 (11), 82 (11), 81 (16), 73 (38), 66 (12), 65 (19), 63 (13), 57 (11), 56 (100), 44 (53), 43 (22), 42 (15), 41 (12), 40 (62).

Typical Experimental Procedure for Heck Coupling of Aryl Iodides with Olefins

A 25-mL, round-bottom flask was charged with iodobenzene (570 μL, 5 mmol), methyl acrylate (540 μL, 6 mmol), triethylamine (978 μL, 7 mmol), catalyst **16d** (204 μg, 0.00025 mmol, 0.01 mol % Pd) and DMF (8 mL). The mixture was stirred at 110 °C in air and the reaction progress was analyzed by GLC. The crude reaction mixture was extracted with water and EtOAc (3× 15 mL). The organic phases were dried, evaporated (15 mm Hg) and the resulting crude product was purified by flash chromatography (hexane/EtOAc) affording methyl cinnamate; yield: 749 mg (92%, 98% pure by GLC analysis).

In order to set up reactions under very highly diluted conditions (10^{-3} mol % Pd) the different catalyst concentrations were obtained by successive dilution of an initial catalyst solution prepared by dissolving catalyst **16d** in toluene (maximum concentration, 3 mg of **16d**/10 mL of toluene to get the catalyst completely dissolved). The catalyst solution was then introduced in the reaction mixture once all the reactants and solvent had been added. In order to avoid undesired "reaction vessel or stirrer catalytic activity" they were always washed with concentrated HNO_3 overnight prior to use in a new catalytic reaction.

Typical Experimental Procedure for Heck Coupling of Aryl Bromides with Olefins

A 25-mL, round-bottom flask was charged with *p*-bromonitrobenzene (412 mg, 2 mmol), styrene (268 μL, 2.4 mmol), potassium carbonate (387 mg, 2.8 mmol), tetrabutylamonium bromide (129 mg, 0.4 mmol), catalyst **16d** (4.079 mg, 0.005 mmol, 0.5 mol % Pd) and DMF (4 mL). The mixture was stirred at 130 °C in air and the reaction progress was analyzed by GLC. The reaction mixture was poured into excess water and extracted several times with ethyl acetate. The organic extract was dried and evaporated to afford (*E*)-4-nitrostilbene; yield: 65% (pure on GLC and ^1H NMR).

Typical Experimental Procedure for Heck Coupling of Aryl Chloride with Olefins

A 25-mL, round-bottom flask was charged with *p*-chloronitrobenzene (318 mg, 2 mmol), methyl acrylate (216 μL, 2.4 mmol), potassium carbonate (387 mg, 2.8 mmol), tetrabutylamonium bromide (129 mg, 0.4 mmol), catalyst **16d** (4.079 mg, 0.005 mmol, 0.5 mol % Pd) and DMF (4 mL). The mixture was stirred at 130 °C in air and the reaction progress was analyzed by GLC. The product was isolated by pouring the reaction mixture into excess water and extracting the aqueous phase several times with ethyl acetate. The organic phases were dried, evaporated (15 mm Hg) and the resulting crude product was purified by flash chromatography (hexane/EtOAc) affording methyl 3-(4-nitrophenyl)-2-propenoate; yield: 267 mg (65%).

Typical Experimental Procedure for Annulation of Alkynes

A 25-mL, round-bottom flask was charged with *o*-iodoaniline (224 mg, 1 mmol), diphenylacetylene (267 mg, 1.5 mmol), potassium carbonate (277 mg, 2 mmol), TBAB (65 mg, 0.2 mmol), catalyst **16d** (4.079 mg, 0.005 mmol) and DMF (4 mL). The mixture was stirred at 130 °C in air and the reaction progress was analyzed by GLC. The product was isolated by pouring the reaction mixture into excess water and extracting the aqueous phase several times with ethyl acetate. The organic phases were dried, evaporated (15 mm Hg) and the resulting crude product was purified by flash chromatography (hexane/EtOAc) affording 2,3-diphenylindole; yield: 116 mg (43%).

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