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Oxime Palladacycles: Stable and Efficient Catalysts for Carbon–Carbon Coupling Reactions

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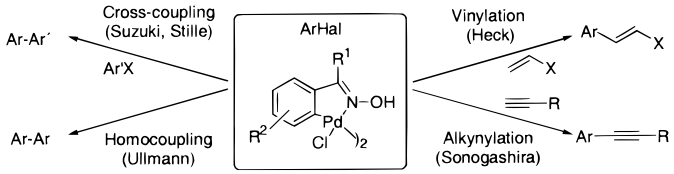
ABSTRACT



Oxime palladacycles are thermally stable complexes not sensitive to air or moisture, easily prepared from very cheap materials, which can be used as versatile and very efficient catalysts for different carbon–carbon bond-forming reactions.

Transition metal-catalyzed coupling reactions are one of the most important processes in organic chemistry and have been extensively studied since they represent a powerful and popular method for the formation of carbon−carbon bonds. This strategy has been applied to the synthesis of many organic compounds, especially the complex natural products, in supramolecular chemistry and in materials science.[1] Organopalladium compounds play an important role in homogeneous catalysis due to their versatility and nontoxicity. They are used in numerous useful transformations for laboratory and industrial chemistry. In particular, carbon−carbon forming reactions represent particularly potent applications of palladium complexes as catalysts. During the past few years, very active systems have been developed in order to improve the stability of palladium-based catalysts and to increase their efficiency. Carbometalated Pd^{II} complexes, especially palladacycles,[2] have emerged as very promising catalysts for C−C bond-forming reactions.

Phospha-palladacycles **1**,[3,4] **2**,[5] **3**,[6] **4**,[7] **5**,[8] and **6**[9] as well as phosphine-free heterocyclic carbenes **7**[3,10] and **8**[11] and also cyclometalated imines **9**[12] have been used in vinylation

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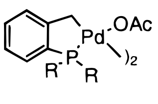
“Heck reaction”,[13] with TONs (turnover number = mol product/mol Pd) of 10^5-10^6. Similarly, the alkynylation of aryl bromides, the so-called “Sonogashira reaction”,[14] has been carried out with Herrmann’s catalyst **1**[3] with more than 10^2 TON. In the case of the cross-coupling process between aryl halides and aryltrialkyltin reagents, the “Stille reaction”,[15] complexes **1**[3] and **4**[7] are excellent catalysts, especially the latter one with more than 10^5 TON. For the coupling of aryl halides with organoboronic acids, the “Suzuki reaction”,[16] compounds **1**,[3,4b] **4**,[7] **7**,[3,10b] and **9**[12b] are adequate catalysts with TONs between 10^2 and 10^6. These palladacycles exhibit higher air and thermal stability than palladium(0) complexes and can operate through a $Pd^{II}-Pd^{IV}$ cycle instead of by the traditional Pd^0-Pd^{II} mechanism.[17]



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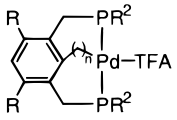

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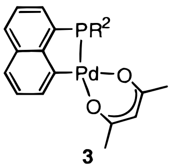

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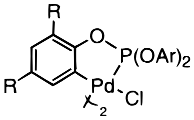

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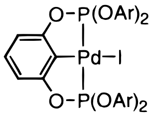

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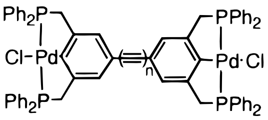
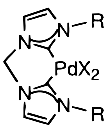


6, n = 1,2



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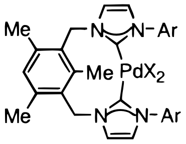

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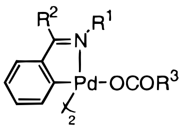

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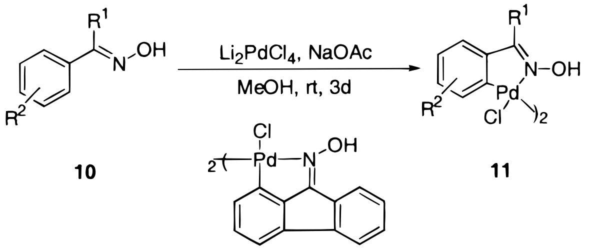
The purpose of our study was to find a suitable, robust, and easily prepared catalyst valid in a wide range of C−C bond-forming processes. Therefore, the initial step was the selection of a potential catalytic system amenable to systematic structural and electronic variation. One of the appealing features of oxime-based palladacycles is that the ligands may be tuned both sterically and electronically in a synthetically straightforward manner by variation of the corresponding ketone precursors. The fact that the aromatic ketoxime-derived palladacycles are extraordinary thermally stable and not sensitive to oxygen or moisture, as well as their ready and economical synthetic access,[18] prompted us to study their activity as catalysts in C−C bond-forming reactions.

For the preparation of the complexes, different oximes **10**, derived from acetophenone, benzophenone, 4,4′-dichlorobenzophenone, 4,4′-dimethoxybenzophenone, and fluorenone, were synthesized and carbopalladated with lithium tetrachloropalladate and NaOAc in methanol at room temperature[18a] to provide chloro bridge complexes **11** in high yields (Scheme 1, Table 1).

Scheme 1. Synthesis of Palladacycles **11**[18a]



11e

Table 1. Synthesis of Palladacycles **11**

entry	no.	R^1	R^2	yield (%)[a]	mp (°C)
1	**11a**	Ph	H	64	139−141[b]
2	**11b**	p-ClC_6H_4	Cl	98	208−210
3	**11c**	p-$MeOC_6H_4$	MeO	92	135−137
4	**11d**	Me	H	92	209−212[c]
5	**11e**	fluorenone		90	>320

[a] Isolated yield. [b] Lit. 150−152 °C.[18a] [c] Lit. 210 °C.[18a]

The arylation of olefins with aryl halides—generally referred to as the “Heck reaction” [13]—was first evaluated with the palladium complexes **11**. To determine the optimum reaction conditions for the catalysts, we chose as a model reaction the coupling between methyl acrylate and PhI in the presence of catalyst **11a** and TEA (triethylamine) (Table 2). The reaction provided quantitative conversions with either DMF or NMP as solvents[19] at 110 °C under air using 10^{-2} mol % of Pd in 2 or 1.5 h, respectively. When using other different solvents such us CH_3CN, THF, dioxane, toluene, or DME, lower conversions were always obtained (23−72%).

Reducing the catalyst loading to 10^{-3} mol % of Pd led to longer reaction times but did not influence the reaction conversion (compare entries 1 and 2, Table 1). As bases, TEA, K_2CO_3, and CsF can be used, with the reaction occuring faster with TEA (Table 2, entries 1, 4, and 5). Similar results were obtained with complexes **11a**, **11b**, **11d**, and **11e**; however, the reaction with the *p*-methoxy-substituted benzophenone complex **11c** was rather slower under the reaction conditions identical to those used for **11a** or **11b** (compare entries 3, 6, and 7, Table 2). *p*-Bromoacetophenone was chosen as a model aryl bromide for the coupling with methyl acrylate to afford very good conversions (Table 2, entries 11 and 12), although Jeffery’s conditions,[20] i.e., higher catalyst loadings and higher tem-

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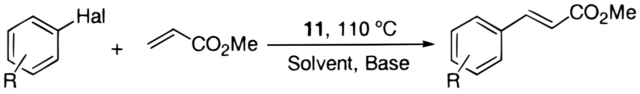
Table 2. Heck Coupling Reactions Catalyzed by Complexes **11**[a]

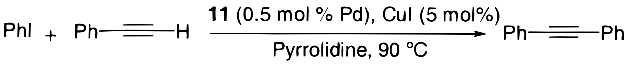


entry	R	Hal	catalyst (mol % of Pd)	solvent	base	*t* (h)	yield (%)[b]	TON
1	H	I	**11a** (0.01)	NMP	TEA	1.5	>99 (92)[c]	10^4
2	H	I	**11a** (0.001)	NMP	TEA	12	>99	10^5
3	H	I	**11a** (0.01)	DMF	TEA	2	98	9800
4	H	I	**11a** (0.01)	NMP	K_2CO_3	4.5	97	9700
5	H	I	**11a** (0.01)	NMP	CsF	3.5	>99	10^4
6	H	I	**11b** (0.01)	DMF	TEA	1.5	>99	10^4
7	H	I	**11c** (0.01)	DMF	TEA	6	85	8500
8	H	I	**11d** (0.01)	DMF	TEA	2	98	9800
9	H	I	**11e** (0.01)	DMF	TEA	1.5	95	9500
10	H	I	**11e** (0.01)	NMP	TEA	2	>99	10^4
11	Ac	Br	**11a** (0.5)	DMF[d]	NaOAC	5	>99 (97)[c]	199
12	Ac	Br	**11e** (0.5)	DMF[d]	NaOAC	3	>99	199

[a] Reaction conditions: 1.0 equiv of ArX, 1.2 equiv of olefine, 1.4 equiv of base. [b] Determined by GC, based on the ArX using decane as internal standard. [c] Isolated yield after flash chromatography. [d] The reaction was carried out at 135 °C in the presence of 20 mol % of Bu_4NCl.

peratures [Bu_4NCl, (20 mol %), NaOAc as base, 0.25 mol % of **11**, and 135 °C] had to be used in this case.

Table 3. Sonogashira Couplings Catalyzed by Complexes **11**[a]



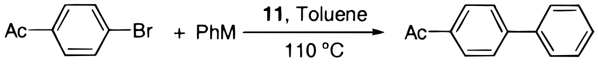
entry	catalyst	*t* (h)	yield (%)[b,c]	TON
1	**11e**	2	71 (68)[d]	142
2	**11a**	2	67 [2]	134
3	**11b**	3	71	142
4	**11c**	5.5	75 [1]	150
5	**11d**	5.5	66	132

[a] Experimental details: 1.0 equiv of PhI, 1.2 equiv of phenylacetylene, catalyst (0.5 mol % of Pd), CuI (5 mol %), 90 °C. [b] Determined by GC, based on PhI using decane as internal standard. [c] The reaction stops at the indicated time; in brackets yield of PhC≡CC≡CPh. [d] Isolated yield after flash chromatography.

The Sonogashira reaction[14] has been investigated using phenylacetylene and phenyl iodide in the presence of catalysts **11** (0.5 mol % of Pd), CuI (5 mol of %), and an amine at 90 °C (Table 3). The influence of the amine was first determined with catalyst **11e** since the choice of the solvent has previously been shown to be critical for the success of the reaction. Thus, when the reaction was performed in the presence of TEA, piperidine, or Hünig's base (diisopropylethylamine), low yields of cross-coupling product (33−52%) and significant amounts of dimeric 1,4-diphenylbuta-1,3-diyne were obtained. However, by using pyrrolidine, and regardless of the catalyst used, the yields were increased up to 75% in 2−5 h with formation of only traces of the undesired diyne (Table 3, entries 1−5). The absence of the cocatalyst, cuprous iodide, resulted in the formation of increased amounts of 1,4-diphenylbuta-1,3-diyne and always led to lower reaction conversions.

In the case of the Stille reaction,[15] trimethyl(phenyl)tin was coupled with *p*-bromoacetophenone at 110 °C in toluene as solvent under neutral conditions. The yields of product were moderate to excellent when catalysts **11a**−**e** were used (Table 4, entries 1−5). Of all the catalysts used, fluorenone-derived palladacycle **11e** gave the best result.

Table 4. Stille[a] and Suzuki[b] Couplings Catalyzed by **11**



entry	M	catalyst	*t* (h)	yield (%)[c]	TON
1	-SnMe_3	**11a**	5	62	21
2	-SnMe_3	**11b**	8	58	19
3	-SnMe_3	**11c**	8	47	16
4	-SnMe_3	**11d**	8	63	21
5	-SnMe_3	**11e**	5	95 (95)[d]	32
6	-B(OH)_2	**11a**	0.5	93[e]	930
7	-B(OH)_2	**11b**	0.5	97[e]	970
8	-B(OH)_2	**11c**	0.5	94[e]	940
9	-B(OH)_2	**11d**	0.5	95[e]	950
10	-B(OH)_2	**11e**	0.5	97[e] (95)[f]	970

[a] Experimental details: 1.0 equiv of aryl bromide, 1.5 equiv of Me_3SnPh, catalyst (3 mol % of Pd). [b] Experimental details: 1.0 equiv of aryl bromide, 1.5 equiv of $PhB(OH)_2$, 2.0 equiv of K_2CO_3, catalyst (0.1 mol % of Pd). [c] Determined by GC, based on the aryl bromide. [d] Isolated yield after flash chromatography. [e] A 2−4% yield of homocoupled product is obtained. [f] Isolated yield after recrystallization.

The coupling of aryl bromides and phenylboronic acid, the "Suzuki reaction",[16] catalyzed by **11** was investigated, and representative results are summarized in Table 4 (entries 6−10). Under standard conditions, these catalysts are very active, and the coupling between *p*-bromoacetophenone and $PhB(OH)_2$ in toluene at 110 °C took place with shorter times (30 min), better yields, and higher TONs than for the Stille reaction.

Finally, encouraged by the results obtained in the previous cross-coupling processes using complexes **11**, we examined their application in other recently described catalytic process for both inter- and intramolecular homocoupling of aryl halides, the "Ullmann reaction". In this methodology, catalytic $Pd(OAc)_2$ (2−5 mol %) in the presence of hydroquinone (HQ) (50 mol %), $CsCO_3$ (100 mol %), and tri-*o*-tolylphosphine or arsine as ligands (2−5 mol %) at temperatures between 75 and 125 °C in DMA are used.[21] Our goal in this case has been to use complex **11e** as catalyst in the intermolecular homocoupling of aryl halides in the absence of phosphine or arsine ligands (Scheme 2). By using 1 mol % of **11e** in the case of phenyl iodide at 110 °C in DMF with HQ (50 mol %) and K_2CO_3 as base (100 mol %), an almost quantitative yield of biphenyl was obtained after 2 h

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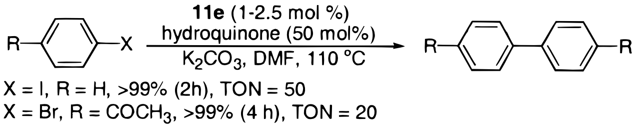
Scheme 2. Ullmann-Type Coupling of Aryl Halides



(85% isolated yield). In the case of *p*-bromoacetophenone, a quantitative yield was obtained by just increasing the catalyst loading to 2.5 mol % under the same reaction conditions.

In summary, this preliminary study has demonstrated that phosphine-free cyclopalladated oxime complexes **11** are very efficient catalysts for a wide range of C−C coupling reactions. The versatility of these catalysts, especially in the case of the fluorenone derived **11e**, is comparable to that of the best systems reported so far. They usually require lower temperatures and shorter reaction times, especially in Heck and Suzuki processes. Their easy synthetic accessibility and structural versatility make these complexes very promising catalysts, and further studies in their applicability to other organic transformations are currently under investigation.

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Supporting Information Available: Experimental procedures for the synthesis of palladium complexes **11** and catalytic processes. This material is available free of charge via the Internet at http://pubs.acs.org.

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