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Controlled mono and double Heck reactions in water catalyzed by an oxime-derived palladacycle

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Dedicated to Professor José Vicente on occasion of his 60th birthday

Abstract—The mono and β , β -diarylation of α , β -unsaturated carbonyl compounds with electron-deficient and electron-rich aromatic iodides in water is described. These reactions are catalyzed by the *p*-hydroxyacetophenone oxime-derived palladacycle **1** by controlling the stoichiometry of the aryl iodide and the alkene as well as the loading of the palladium catalyst. This one-pot protocol is performed in refluxing water and (dicyclohexyl)methylamine as base under thermal or microwave conditions and in the absence of an inert atmosphere.

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The use of water as solvent in organic reactions is an important goal for the development of environmentally and technologically safe industrial-scale processes.¹ Palladium-promoted reactions in aqueous media have important advantages concerning catalyst separation from the organic products and increasing selectivity and efficiency. The well-known palladium-catalyzed alkenylation reaction of aromatic halides and other aromatic substrates, the so-called Heck-Mizoroki reaction, has emerged as one of the most powerful synthetic tools in organic synthesis. However, it has not been extensively studied in aqueous media.² Beletskaya and co-workers used in their seminal work ligand-free palladium(II) salts for the Heck reaction in pure water or in aqueous organic solvents in the presence of inorganic bases for hydrophilic materials.³ In addition, palladium(II) acetate is the catalyst of choice in phosphane-free⁴ or in the presence of a phosphane under phase-transfer catalysis (PTC)⁵ in aqueous environments. Moreover, palladium on carbon under PTC in the presence of a reducing agent has been shown as an appropriate catalyst for the arylation of styrene in water.⁶ Recently, a di-2-pyridylmethylamine-based palladium chloride complex7 and a cyclopalladated ferrocenylimine⁸ have been found

to be good phosphane-free catalyst for Heck reactions in water. Several groups have been working in the development of water-soluble ligands, such as sulfonated aryl phosphanes.⁹ The presence of water has been found to be beneficial when this alkenylation reaction was carried out in organic solvents, such as *N*-methylpyrrolidone (NMP)¹⁰ and also to promote the formation of palladium nanoparticles.¹¹

The classical intermolecular Heck reaction is mainly limited to the monoarylation of terminal alkenes.² The synthesis of multisubstituted alkenes by β , β -diarylation has been scarcely investigated.¹² In the pioneering work of Heck and co-workers was described the diarylation of methyl acrylate with an excess of iodobenzene by using $Pd(OAc)_2$ and $P(o-tol)_3$ under acetonitrile reflux for 21 h to give 3,3-diphenylacrylate in 78% yield.¹³ Acrylonitrile suffers easily β , β -diarylation when a montmorillonite ethylsilyldiphenylphosphanepalladium(II) anchored dichloride complex is used as catalyst.14 Recent examples about β , β -diarylation of *n*-butyl acrylate have been carried out in ionic liquids with benzothiazole carbene¹⁵ and bisimidazole¹⁶ derived palladium(II) complexes. Controlled mono and diarylation of acrylates can be performed under high pressure conditions.¹⁷ However, the development of an efficient process for the control of the mono and diarylation of terminal alkenes in water would be desirable. We have recently shown that oximederived palladacycles are versatile precatalysts in Heck, Suzuki, Stille, Sonogashira, sila-Sonoghasira, Ullmann

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and Rossi reactions in organic solvents.¹⁸ Moreover, these type of palladacycles were active in neat water for Suzuki couplings of aryl and alkyl boronic acids with aryl bromides and chlorides as well as with allylic and benzylic chlorides.¹⁹ We report now that an oxime-derived palladacycle is an appropriate precatalyst for the controlled mono and β , β -diarylation of terminal alkenes under very simple reaction conditions in neat water.

For the Heck reactions in water we studied different bases using $10^{-2} \mod \%$ Pd of complex 1, which was a very efficient catalyst in the Suzuki reaction carried out in aqueous media.¹⁹ The monoarylation reaction of tertbutyl acrylate (2a) with 1 equiv of *p*-chloroiodobenzene under water reflux was studied in the presence of different secondary and tertiary amines, such as diisopropylamine,²⁰ dicyclohexylamine or (dicyclohexyl)methylamine,²¹ and triethylamine (Scheme 1 and Table 1, entries 1–4). The reaction was faster (3 h) (Table 1, entry 4) in the presence of Cy_2NMe giving product 3ab in a high TON of 59,000 (Table 1, entry 5). When the reaction was carried out under microwave irradiation²² at 120 W and 120 °C,²³ the monoarylation took place in only 10 min with similar TON but much higher TOF (up to 42,000) (Table 1, entry 6). When $Pd(OAc)_2$ was used instead of palladacycle 1 either under thermal or microwave conditions, similar results were achieved (Table 1, compare entries 4 and 7 or 6 and 8, respectively). For the diarylation process of 2a to give compound **4aa** 2 equiv of iodobenzene and 3 equiv of (dicyclohexyl)methylamine under water reflux were the best reaction conditions, being necessary to increase the amount of catalyst **1** to 1 mol% in order to obtain good conversions (Scheme 1 and Table 1, entries 9–11). Other bases such as triethylamine or diisopropylamine failed and Pd(OAc)₂ gave very poor conversions or no reaction under microwave conditions (Table 1, entries 12 and 13).

The scope of the mono and diarylation reactions under water reflux was studied with different α,β -unsaturated carbonyl compounds and activated and deactivated iodides using palladacycle 1 as catalyst and (dicyclohexyl)methylamine as base (Scheme 1 and Table 2). For *tert*-butyl acrylate (2a) the mono and diarylation reaction with activated aryl iodides (Table 2, entries 3–6) provide compounds 3 and 4 using a lower catalyst loading than iodobenzene (Table 2, entries 1 and 2) or deactivated aryl iodides (Table 2, entries 7 and 8). In the case of diarylation with p-chloroiodobenzene, diisopropylamine has to be used as base because (dicyclohexyl)methylamine gave also the corresponding product 4,4'-dichlorobiphenyl homocoupling as byproduct (Table 2, entry 4). When $Pd(OAc)_2$ was used as catalyst the monoarylation works nicely also with p-methoxyiodobenzene (Table 2, entry 9). However, the diarylation failed with p-fluorobenzene²⁴ after 23 h reaction time (Table 2, entry 10) and in the case of



Scheme 1.

 Table 1. Mono and diarylation of tert-butyl acrylate: reaction conditions study

Entry	ArI (equiv)	Cat. (mol% Pd)	Amine	Reaction conditions ^a	Time	Yield (%) ^b	TON	TOF (h^{-1})
1	$4-ClC_{6}H_{4}I(1)$	1 (1.1×10^{-2})	<i>i</i> -Pr ₂ NH	Thermal	24 h	63°	5727	239
2	$4-ClC_{6}H_{4}I(1)$	$1(10^{-2})$	Et ₃ N	Thermal	14 h	89 (83) ^c	8900	636
3	$4-ClC_{6}H_{4}I(1)$	$1(10^{-2})$	Cy ₂ NH	Thermal	6 h	94°	9400	1567
4	$4-ClC_{6}H_{4}I(1)$	$1(1.1 \times 10^{-2})$	Cy ₂ NMe	Thermal	3 h	96 (94) ^c	8727	2909
5	$4-ClC_{6}H_{4}I(1)$	$(10^{-3})^d$	Cy ₂ NMe	Thermal	24 h	59°	59,000	2458
6	$4-ClC_{6}H_{4}I(1)$	$1(1.3 \times 10^{-2})$	Cy ₂ NMe	μν	10 min	91 (87) ^c	7000	42,000
7	$4-ClC_{6}H_{4}I(1)$	$Pd(OAc)_2 (1.1 \times 10^{-2})$	Cy ₂ NMe	Thermal	3 h	83°	7545	2515
8	$4-ClC_{6}H_{4}I(1)$	$Pd(OAc)_2 (1.2 \times 10^{-2})$	Cy ₂ NMe	μν	10 min	98 (88) ^c	8167	49,000
9	PhI (2)	1 (1)	Cy ₂ NH	Thermal	14 h	58 ^e	58	4
10	PhI (2)	1 (1)	Cy ₂ NMe	Thermal	13 h	65 (66) ^e	66	5
11	PhI (2)	1 (1)	Cy ₂ NMe	μν	10 min	31°	31	186
12	PhI (2)	$Pd(OAc)_2$ (1)	Cy ₂ NMe	Thermal	14 h	13 ^e	13	1
13	PhI (2)	$Pd(OAc)_2$ (1)	Cy ₂ NMe	μν	10 min	e	_	

^a Reaction conditions see typical procedure.

^b Determined by GC based on the ArI using decane as an internal standard. In parenthesis yields after purification.

^c For compound **3ab**.

^d A 2×10^{-5} M solution (0.5 mL) of palladacycle 1 in *N*,*N*-dimethylacetamide (DMAc) was added.

^e For compound 4aa.

Table 2. Mono and diarylation reactions in water with aryl iodides

Entry	Olefin	Cat. (mol% Pd)	Time (h)	Product				
				No.	Z	Ar	Yield (%) ^a	
1	2a	1 (10 ⁻²)	3	3aa	CO ₂ -t-Bu	Ph	87	
2	2a	1 (1)	13	4 aa	CO ₂ -t-Bu	Ph	91	
3	2a	1 (1.1×10^{-2})	3	3ab	CO ₂ -t-Bu	$4-ClC_6H_4$	94	
4	2a	$1 (10^{-1})^{b}$	22	4ab	CO ₂ -t-Bu	$4-ClC_6H_4$	89	
5	2a	1 (10 ⁻²)	22	3ac	CO ₂ - <i>t</i> -Bu	$4-FC_6H_4$	85	
6	2a	1 (10 ⁻¹)	14	4ac	CO ₂ -t-Bu	$4-FC_6H_4$	92	
7	2a	1 (1.2×10^{-2})	14	3ad	CO ₂ -t-Bu	4-MeOC ₆ H ₄	87	
8	2a	1 (1)	14	4ad	CO ₂ -t-Bu	4-MeOC ₆ H ₄	75	
9	2a	$Pd(OAc)_2 (2 \times 10^{-2})$	14	3ad	CO ₂ -t-Bu	4-MeOC ₆ H ₄	84	
10	2a	$Pd(OAc)_2 (10^{-1})$	23	4ac	CO ₂ - <i>t</i> -Bu	$4-FC_6H_4$	0	
11	2a	$Pd(OAc)_2$ (1)	14	4ad	CO ₂ -t-Bu	4-MeOC ₆ H ₄	34	
12	2b	$1 (10^{-1})$	14	3ba	$CONMe_2$	Ph	96	
13	2b	1 (1)	14	4ba	CONMe ₂	Ph	77	
14	2c	1 (1)	9	3ca	CN	Ph	94°	
15	2c	$1 (10^{-1})$	23	4ca	CN	Ph	86	
16	2d	1 (8.6×10^{-3})	23	3da	COMe	Ph	69 ^d	
17	2d	1 (0.5)	8	4da	COMe	Ph	41 ^e	

^a Yield after flash chromatography (hexane/EtOAc).

^bDiisopropylamine was used as base.

^c A Z/E:1/4 mixture was obtained.

^d 5% of **4da** and 5% of **5da** were isolated.

e 53% of 5da was isolated.

p-methoxyiodobenzene a lower yield than using palladacycle 1 was observed (Table 2, compare entries 8 and 11). In the case of N,N-dimethylacrylamide (2b) and acrylonitrile (2c) the mono and diarylation with iodobenzene could also be controlled (Table 2, entries 12-15). Surprisingly, for acrylonitrile the diarylation²⁵ is more favorable than the monoarylation and in this case the amount of catalyst has to be higher for the later process (Table 2, entries 14 and 15). When methyl vinyl ketone was used as alkene in the monoarylation process also 10% of a 1/1 mixture of diarylation products 4da and 5da was obtained (Table 2, entry 16). The diarylation of this ketone gave a ca. 1/1 mixture of products 4da and 5da. Saturated ketone 5da results by in situ conjugated addition on the unsaturated ketone 3da.²⁶ On the other hand, both mono and diarylation processes in neat water failed when aryl bromides instead of aryl iodides were used.



The catalyst **1** remains active upon addition of more substrates in both mono and diarylation processes. In the case of the monoarylation of *tert*-butyl acrylate with *p*-chloroiodobenzene (see conditions in Table 2, entry 3) total conversion was observed during four subsequent cycles. Each cycle was performed in situ by addition of the reagents and water (1 mL) and considered complete after 3 h reaction time (monitorized by GLC). For the diarylation reaction between both substrates (Table 2, entry 4) using higher catalyst **1** loading (1 mol% Pd) also total conversion after 13 h was obtained during four

cycles after subsequent addition of the substrates and water (1 mL).

In conclusion, oxime-derived palladacycle **1** or $Pd(OAc)_2$ are appropriate catalysts for the monoarylation of α , β -unsaturated carbonyl compounds in water using (dicyclohexyl)methylamine as base either under thermal or microwave conditions, whereas for diarylation reactions thermal conditions have to be used and palladacycle **1** is the catalyst of choice.

Typical experimental procedure: A 15 mL Ace pressure tube was charged with the aryl iodide (2 mmol), the alkene (3 mmol), (dicyclohexyl)methylamine (0.642 mL, 3 mmol), the catalyst (0.01-1 mol % Pd) and water (3mL) for monoarylation reactions. For diarylation the following amounts were used, aryl iodide (1 mmol), alkene (0.5 mmol), (dicyclohexyl)methylamine the (0.321 mL, 1.5 mmol), the catalyst (0.01–1 mol % Pd, see Tables 1 and 2) and water (2 mL). The mixture was heated at 120 °C and monitorized by GLC. The reaction mixture was cooled and poured in EtOAc (40 mL). The organic phase was washed with 2 M HCl $(2 \times 30 \text{ mL})$ and water $(2 \times 30 \text{ mL})$, dried (Na_2SO_4) , and the solvent evaporated to afford the corresponding crude olefin which was purified by recrystallisation or flash chromatography (hexane/EtOAc) to afford pure compounds 3 or $\tilde{4}$.²⁷

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- 24. Similar result has been observed in ionic liquids as solvents with bisimidazole palladium complexes.¹⁶
- 25. The Heck reaction of acrylonitrile with iodobenzene in the presence of tri-*n*-butylamine at 100 °C with montmorillonite-ethylsilyldiphenylphosphane palladium(II) dichloride as catalyst gave 3,3-diphenylacrylonitrile (**4ca**) exclusively.¹⁴
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