Anais da Academia Brasileira de Ciências (2018) 90(1 Suppl. 2): 1273-1278
(Annals of the Brazilian Academy of Sciences)
Printed version ISSN 0001-3765 / Online version ISSN 1678-2690
http://dx.doi.org/10.1590/0001-3765201820170858
www.scielo.br/aabc | www.fb.com/aabcjournal

New Palladacycle-Derived Acylhydrazones as Pre-catalysts in Mirozoki-Heck Coupling and Oxyarylations

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Manuscript received on October 25, 2017; accepted for publication on January 12, 2018

ABSTRACT

New acylhydrazone-based palladacycles are prepared and evaluated as pre-catalysts in Mirozoki-Heck and oxyarylation reactions.

Key words: acylhydrazone, palladacycle, Mirozoki-Heck reaction, oxyarylation.

INTRODUCTION

Palladacycles were discovered in the mid-1960s as intermediates in palladium- mediated transformations and have been employed as active intermediates in cascade transformations leading to complex molecular architectures (Beletskaya and Cheprakov 2004, Dupont et al. 2005).

Since the preparation of the cyclopalladate tri-*o*-tolyl-phosphine complex reported by Herman (Hermann et al. 1995, 1999) and its use as a pre-catalyst for palladium-catalyzed Mirozoki-Heck and other cross-coupling reactions, the use of palladacycles has experienced tremendous growth (Beletskaya and Cheprakov 2004, Dupont et al. 2005).

Their high thermal stability in the solid state, easy preparation and ready modulation of both steric and electronic properties make them affordable tools in organic synthesis. In fact, a large number of new palladacycles have been prepared and used as pre-catalysts (Alonso et al. 2000, Nájera 2016).

Despite some suggestion of a mechanism involving Pd(II) and Pd(IV) species (Shaw et al. 1998a, Shaw 1998), they are considered as a source of *in situ* formed Pd(0) nanoparticles, which have been successfully used in several coupling reactions in low catalytic loading. In addition, palladacycles can be prepared in water and do not require the presence of ligands, making their use very attractive (Beletskaya and Cheprakov 2004, Dupont et al. 2005).

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* Contribution to the centenary of the Brazilian Academy of Sciences.

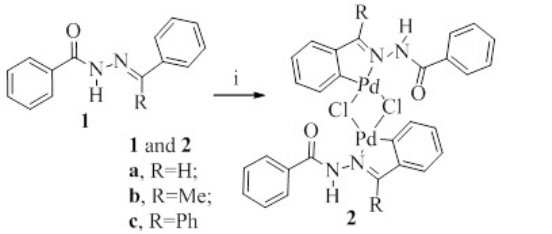
Although some hydrazone-based palladacycles are known in the literature and promote Suzyki-Miyaura and Mirozoki-Heck coupling reactions (Cardenas and Echavarren 1995, Nagy et al. 2005), herein we describe the first synthesis and application of acyl-hydrazone-based paladacycles as pre-catalysts in Mirozoki-Heck and oxyarylation reactions.

DISCUSSION AND RESULTS

Acylhydrazones (**1a-c**) are easily prepared by the reaction of acylhydrazines with aromatic aldehydes and have been extensively used as a platform to construct interesting biologically active compounds (Fraga and Barreiro 2006).

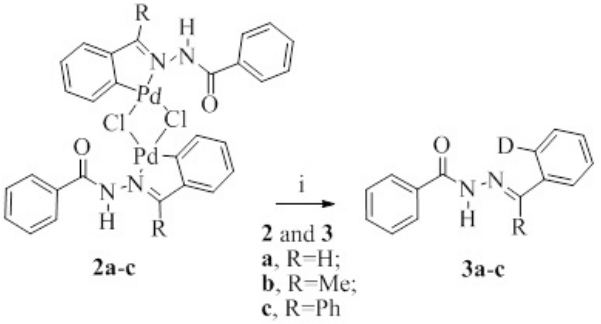
The new palladacycles **2a-c** were prepared by electrophilic C-H activation of acylhydrazones **1a-c** with Li_2PdCl_4 in methanol in the presence of NaOAc as the base at room temperature (Figure 1) (Alonso et al. 2002). Compounds **2a-c** precipitated from the reaction medium and were obtained as yellowish stable solids after filtration.

Once ^{1}H NMR spectra are complex to analyze the structures of **2a-c** were determined by indirect way. Palladacycles **2a** and **2c** were reduced with $NaCNBD_3$ in THF/MeOH (Figure 2) (Alonso et al. 2002) leading to the respective deuterated acylhydrazones **3a** and **3c**, which were characterized by GC/MS and ^{1}H NMR. Also, the palladacycle **2b** was reduced under the same conditions, yielding the acylhydrazone **3b** (GC/MS).



i, Li_2PdCl_4, NaOAc, MeOH, r.t., 3 days. **2a**, 63%; **2b**, 57%, **2c**, 67%

Figure 1 - Preparation of the palladacycles **2a-c**.



i. $NaBD_3CN$, THF/MeOH, 0 °C-r.t., 1 h

Figure 2 - Reduction of the palladacycles **2a-c**.

A fragment of the oxonium ion at m/z = 105 was the base peak in all three cases (Figure 3). Since this fragment does not present deuterium in its structure, the Pd-C bond in palladacycles **2a-c** must be located at the B ring. Deuterated acylhydrazones **3a** and **3c** led to a deuterated fragment at m/z = 224, while for **3b** a fragment was observed at m/z = 147, by releasing a deuterated phenyl group. These analyses clearly indicate that the deuterium is located in the **B**-ring, in accordance with the proposed structures of **2a-c**.

To demonstrate the efficiency of these new acylhydrazone-based palladacycles, they were evaluated in the Mirozoki-Heck reaction between iodobenzene (**4**) and methyl acrylate (**5**). The yield of methyl cinnamate (**6**) and the major reaction conditions studied are shown in Figure 4 and Table I. Triethylamine was used as the base and after 10 h at 110 °C in the presence of 0.1 mol% Pd source**,** **6** was obtained in excellent yield, regardless of the pre-catalyst used (entries 1-3, Table I). Similar yields were obtained in the presence of 0.001 mol% of **2a-c**, but using a more prolonged reaction time (entries 3-6, Table I). Similar results were obtained when DIPEA was used as the base (entries 7 and 8, Table I) but yields decreased in the presence of Na_2CO_3 (entries 9-11, Table I). The yields were still good when MeCN or NMP were employed as solvents (entries 12-16, Table I). However, no reaction was observed when the reaction was

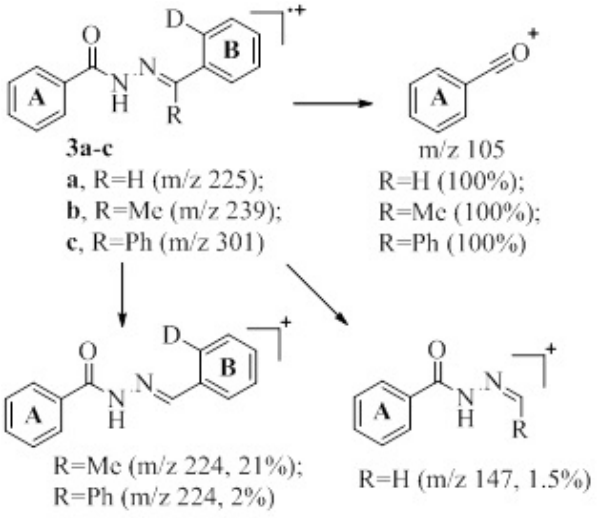


Figure 3 - Proposed mechanism for the fragmentation of **3a-c**.

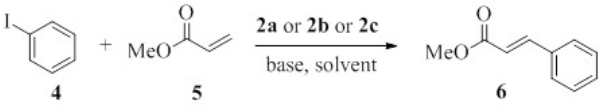


Figure 4 - Mirozoki-Heck reaction of **4** and **5** in palladacycles **2a-c** as pre-catalysts.

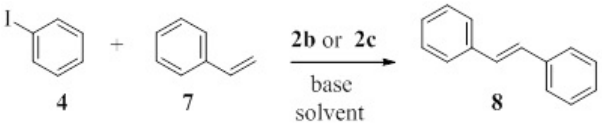


Figure 5 - Mirozoki-Heck reaction of **4** and **7** in palladacycles **2a**,**b**.

conducted in the mixture DIPEA-water (data not shown).

Next, we studied the Mirozoki-Heck reaction between **4** and styrene (**7**), shown in Figure 5 and Table II. Stilbene (**8**) was obtained in reasonable yield when 0.1 mol% **2b** or **2c** were used as pre-catalyst (entries 1 and 2, Table II) but the yield decreased when 0.001 mol% of pre-catalyst was employed (entries 3 and 4, Table II).

Finally, we turned our attention to a more challenging transformation, the oxyarylation reaction. The first catalytic version of the oxyarylation reaction was reported (Larock 1998) under conditions that favored the neutral pathway. Kiss et al. (2003) reported the use of silver carbonate as base, conditions where the cationic mechanism is favored.

The scope of this reaction in the presence of Ag_2CO_3 was studied by our group and a cationic palladacycle formed in the migratory insertion step could be intercepted by ESI-MS and characterized by ESI-MS/MS (Buarque et al. 2010). As the carbopalladation step occurs with the attachment of the aryl group and the palladium atom in the same face of the olefin, the *cis*-stereoselectivity observed in oxyarylation reaction can be understood by

TABLE I
Yields and main conditions for reactions shown in Figure 4.

entry	Solvent	Base	Pd(mol%)	T(°C)	Time (h)	Yield (%)
1	DMF	TEA	0.1(**2a**)	110	10	96
2	DMF	TEA	0.1(**2b**)	110	10	98
3	DMF	TEA	0.1(**2c**)	110	10	98
4	DMF	TEA	0.001(**2a**)	110	24	80
5	DMF	TEA	0.001(**2b**)	110	24	95
6	DMF	TEA	0.001(**1c**)	110	24	95
7	DMF	DIPEA	0.001(**2a**)	110	24	85
8	DMF	DIPEA	0.001(**2b**)	110	24	80
9	DMF	Na_2CO_3	0.001(**2a**)	110	24	65
10	DMF	Na_2CO_3	0.001(**2b**)	110	24	72
11	DMF	Na_2CO_3	0.001(**2c**)	110	24	70
12	MeCN	TEA	0.001(**2a**)	80	24	90
13	MeCN	TEA	0.001(**2b**)	80	24	92
14	MeCN	TEA	0.001(**2c**)	80	24	92
15	NMP	TEA	0.001(**2b**)	110	24	80
16	NMP	TEA	0.001(**1c**)	110	24	75

TABLE II
Yields and main conditions for the reaction shown in Figure 5.

entry	Solvent	Base	Pd (mol%)	T (°C)	Time (h)	Yield (%)
1	DMF	TEA	0.1(**2b**)	110	24	67
2	DMF	TEA	0.1(**2c**)	110	24	60
3	DMF	TEA	0.001(**2b**)	110	24	50
4	DMF	TEA	0.001(**2c**)	110	24	45

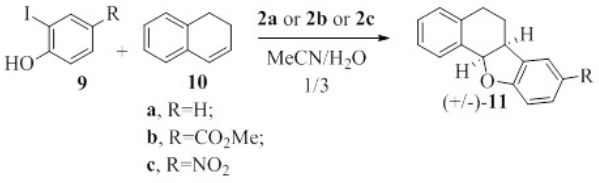


Figure 6 - Oxyarylation reaction of **10** with **9** in the presence of palladacycles **2a-c**.

the retention of configuration in the course of the formation of O-C bond in the reductive elimination step (Buarque et al. 2010).

The Najera's palladacycle also catalyzed these reactions, but the mechanism was not studied under these conditions (Leão et al. 2011). The use of PEG-400 as solvent and additive was also reported (de Moraes et al. 2015).

The oxyarylation reaction of dihydronaphthalene **10** with *ortho*-iodophenols **9a-c** was used in order to evaluate the efficiency of the palladacycles **2a-c**. (Figure 6 and Table III). Interestingly, these reactions did not proceed when performed in DMF. However, compounds **11a-c** were obtained in reasonable yields using the mixture MeCN-H_2O (MeCN-H_2O =1/3), irrespective of the pre-catalyst used (entries 1-5, Table III). Yields for **11a** are higher than that obtained with Najera's palladacycle (35% under thermal conditions, data not shown) (Leão et al. 2011). In contrast, for reactions using silver carbonate as base (de Moraes et al. 2015) the yields did not depend on the pattern of substitution in **9**.

CONCLUSIONS

In summary, we describe the synthesis of new acylhydrazone-based palladacycles and their application as efficient pre-catalysts in Mirozoki-Heck and oxyarylation reactions in reasonable to good yield using low catalytic load.

TABLE III
Yields and main conditions for the reaction shown in Figure 6.

entry	ArI	Pd (1mol%)	Product	T (°C)	Time (h)	Yield (%)
1	**9a**	**2a**	**11a**	120	12	50
2	9a	2b	11a	120	12	55
3	**9a**	**2c**	**11a**	120	12	56
4	**9b**	**2c**	**10b**	120	12	52
5	**9c**	**2c**	**10c**	120	12	53

EXPERIMENTAL SECTION

GENERAL

All the reagents and solvents were purchased from Aldrich Chem. Co. and used without purification. Melting points were determined with a Thomas–Hoover apparatus. Column chromatography was performed on flash silica 0.035-0.070 mm (Acros). IR spectra were obtained in an IR Prestige-21 Shimadzu. NMR spectra were recorded on a Varian 400 (400 MHz) spectrometer. Low-resolution mass spectra were obtained from a GCMS-QP 5000 Plus Shimadzu.

SYNTHESIS OF ACYLHYDRAZONES **1a-c**

To a solution of benzohydrazide (0.3 g; 2.20 mmol) in absolute ethanol (5 mL) containing three drops of 37% hydrochloric acid, was added 2.31 mmol of the appropriated aromatic carbonyl. The mixture was stirred at 70 °C for 8 hours when an extensive precipitation occurs. The mixture was poured into cold water, neutralized with 10% aqueous sodium bicarbonate solution and the precipitate was filtered off and washed several times with petroleum ether.

Acylhydrazone 1a: 55%; Mp 205-206 °C. ^{1}H RMN (400 MHz, DMSO-d_6), d(ppm): d11.85 (s, 1H), 8.48 (s, 1H), 7.93 (d, *J*= 7.35 Hz, 2H), 7.74 (d, *J*= 6.31 Hz, 2H), 7.62–7.46 (m, 6H).

Acylhydrazone 1b: 30%; Mp 150-151 ºC. ^{1}H NMR (400 MHz, DMSO-d_6), d(ppm): δ 10.75 (s, 1H), 7.86 (s, 4H), 7.64 – 7.35 (m, 6H), 2.35 (s, 3H). MS (70 eV): m/z= 238 (7), 223 (23), 105 (100).

Acylhydrazone 1c: 67%; Mp 113-114 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.46 (m, 3H), 7.42 – 7.36 (m, 4H), 7.34 – 7.26 (m, 9H). MS (70 eV): m/z= 300 (30), 223 (9), 195 (7), 165 (10), 105 (100).

SYNTHESIS OF PALLADACYCLES **2a-c**

To a solution of Li_2PdCl_4 (0.99 mmol) in methanol (2 mL) was added a methanolic solution (3 mL) of the appropriated acylhydrazone **1a-c** (0.99 mmol) and sodium acetate (0.081 g, 0.99 mmol). The solution was stirred for 3 days at room temperature. After this time, water (10 mL) was added and the corresponding cyclopalladated complexes precipitated were filtered off. The compounds **2a-c** were obtained with yields between 73-79%.

Compound **2a**: 78%; Mp 180-182 ºC. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.97 (d, *J* = 7.2 Hz, 6H), 7.63-7.58 (m, 5H), 7.54 – 7.50 (m, 7H), 7.08 (sl, 5H).

Compound **2b**: 73%; Mp 215-216 ºC. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.84 (s, 1H), 8.53 – 8.24 (m, 22H), 8.20-8.00 (m, 3H), 7.83 (dd, *J* = 72.3, 7.0 Hz, 37H), 7.68 – 7.46 (m, 9H), 7.22 – 6.95 (m, 3H), 3.33 (s, 6H).

Compound **2c**: 79%; Mp 206-209 ºC. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.25 (sl, 2H), 7.85 (dd, *J* = 14.4, 6.8 Hz, 1H), 7.74 (d, *J* = 6.7 Hz, 6H), 7.60 – 7.34 (m, 16H), 7.05 (d, *J* = 28.9 Hz, 3H), 6.78 (s, 2H).

REDUCTION OF COMPLEXES **2a-c** WITH SODIUM CYANOBORODEUTERIDE

To a mixture of the appropriated complex **2a-c** (0.125 mmol) in THF (2.5 mL) and MeOH (1.25 mL), was added portionwise sodium cyanoborodeuteride (0.016 g, 0.250 mmol) at 0 ºC and the mixture was stirred for 1 hour and allowed to reach room temperature. The black precipitate was filtered off, the solvents were evaporated and the residue hydrolyzed with water, extracted with ethyl acetate, the organic layer dried with Na_2SO_4, and evaporated. The deuterated acylhydrazones (**3a**, **3b** and **3c**) were obtained in 78, 73 and 63% yields, respectively.

Deuterated acylhydrazone of benzaldehyde 3a: 78%; Mp 138-140 ºC. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.85 (s, 1H), 8.48 (s, 1H), 7.93 (d, *J* = 7.4 Hz, 2H), 7.74 (d, *J* = 6.3 Hz, 2H), 7.54 (ddd, *J* = 30.9, 19.0, 7.0 Hz, 7H). MS (70 eV): m/z= 225 (2%), 224 (4%), 121 (20%), 105 (100), 77 (26).

Deuterated acylhydrazone of acetophenone 3b: 73%; Mp 200-201 ºC. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.77 (s, 1H), 7.88 (sl, 2H), 7.62 – 7.55 (m, 1H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.43 (s, 3H), 2.37 (s, 3H). MS (70 eV): m/z= 239 (4), 224 (19), 105 (100), 77 (46).

Deuterated acylhydrazone of benzophenone 3c: 63%; Mp 100-102 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.71 (d, *J* = 5.2 Hz, 1H), 7.62 – 7.56 (m, 5H), 7.48 (dd, *J* = 12.7, 7.4 Hz, 2H), 7.39 – 7.33 (m, 6H). MS (70 eV): m/z= 301 (10), 300 (10), 223 (5), 165 (6), 105 (100), 77 (42).

CONCLUSIONS

In summary, we describe the synthesis of new acylhydrazone-based palladacycles and their application as efficient pre-catalysts in Mirozoki-Heck and oxyarylation reactions in reasonable to good yield using low catalytic load.

ACKNOWLEDGMENTS

The authors thank Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Ensino Superior (CAPES), Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) and Financiadora de

Estudos e Projetos (FINEP) for financial support and fellowships.

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