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Chemoselective Heck arylation of acrolein diethyl acetal catalyzed by an oxime-derived palladacycle

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Dedicated to Professor Jean Pierre Genêt on the occasion of his 60th anniversary

Abstract—A dimeric 4-hydroxyacetophenone oxime-derived palladacycle has been used as a very efficient precatalyst for the chemoselective arylation of acrolein diethyl acetal to give either cinnamaldehyde derivatives or 3-arylpropanoate esters by proper choice of the reaction conditions. The synthesis of cinnamaldehyde derivatives can be performed by Heck reaction of acrolein diethyl acetal with iodo-, bromo- or chloroarenes in *N*,*N*-dimethylacetamide (DMA) using K_2CO_3 as base at 120 °C and tetra-*n*-butylammonium acetate (TBAA) and KCl as additives, followed by acid workup. In the case of 3-arylpropanoate esters the corresponding arylation of acrolein diethyl acetal with iodoarenes can be performed at 90 °C in aqueous DMA using (dicylohexyl)methylamine as base, whereas for bromoarenes the reaction has to be performed at 120 °C using tetra-*n*-butylammonium bromide (TBAB) as additive. Alternatively, this process can be performed under microwave irradiation. These couplings take place in good yields and with lower catalyst loading than with palladium(II) acetate as well as in shorter reaction times and with lower excess of acrolein diethyl acetal.

1. Introduction

Cinnamaldehyde derivatives are important compounds present in nature and widely used not only in food and cosmetic industries[1] but also exhibit antifungal,[2] antibacterial,[3] antitermitic,[4] insecticidal,[5] and antitumor[6] activities. For instance, 2′-hydroxycinnamaldehyde, isolated from the stem bark of *Cinnamonum cassia* Blume (Lauraceae), has shown in vitro activities on farnesyl transferase, angiogenesis, immunomodulation, cell–cell adhesion and cytotoxicity against tumor cell lines.[6,7] Other cinnamaldehyde derivatives have been used for the preparation of new materials in nonlinear optics.[8] A straightforward strategy for the diastereoselective preparation of cinnamaldehyde derivatives is the Heck–Mizoroki reaction[9] of acrolein with aryl halides. However, acrolein polymerizes in basic media at elevated temperatures under the typical Heck reaction conditions.[10] Jeffery has reported this coupling at room temperature for some aryl iodides by using phase-transfer catalysis conditions,[11] but long reaction times are required and low yields were obtained with deactivated iodoarenes, whereas the reaction failed with aryl bromides.[12,13] In order to avoid polymerization, Zebovitz and Heck studied the arylation of acrolein acetals with aryl iodides and bromides using $Pd(OAc)_2$/(*o*-tol)$_3$P as catalysts, Et_3N as base in DMF at 100 °C, but mixtures of cinnamaldehyde acetals and 3-arylpropanoate esters were obtained.[10] This result is due to the two possible palladium hydride eliminations from the carbopalladated intermediate (Scheme 1). Using these Heck conditions double coupling has been successfully performed with 1,4-dibromo-2,5-dimethoxybenzene and acrolein dimethyl acetal.[14] However, under these reactions conditions 3-amino-4-iodopyridine gave mixtures of competitive vinylic substitution product and ester derivative, but when using Jeffery's protocol [$Pd(OAc)_2$ (5 mol%), $NaHCO_3$, tetra-*n*-butylammonium chloride (TBAC), DMF, 70 °C] and a fast aqueous workup a clean arylation of acrolein dimethyl acetal occurred.[15] Unfortunately, the coupling with 3-halo-3-aminopyridines failed under the last reaction conditions. Very recently, Cacchi et al. have found after a careful screening of the reaction conditions that aryl iodides and bromides can be coupled chemoselectively with acrolein diethyl acetal to yield cinnamaldehyde derivatives [$Pd(OAc)_2$ (3 mol%), tetra-*n*-butylammonium acetate (TBAA), K_2CO_3, KCl, DMF, 90 °C][13] or ethyl 3-arylpropanoates [$Pd(OAc)_2$ (3 mol%), TBAC, Bu_3N, DMF, 90 °C].[16]

Keywords: Heck reaction; Cinnamaldehydes; 3-Arylpropanoates/acrolein; Palladacycles.
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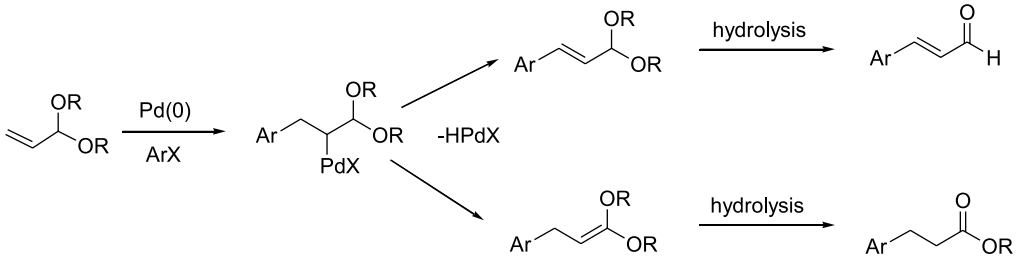
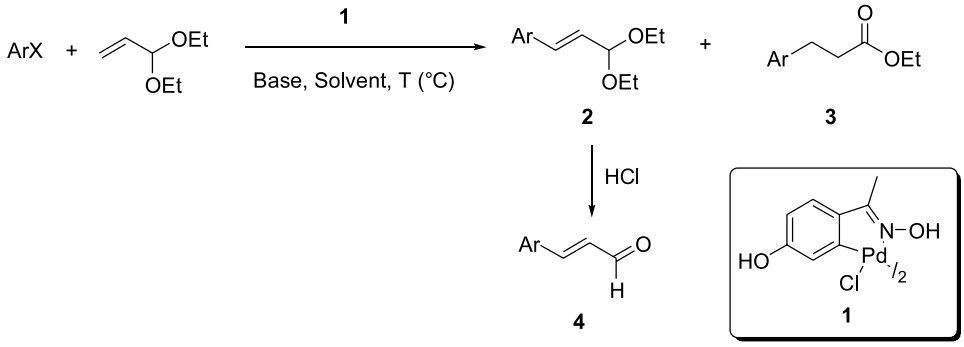


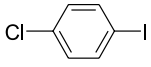
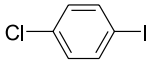
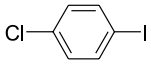
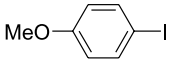
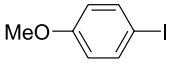
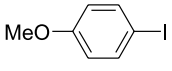
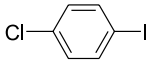
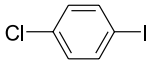
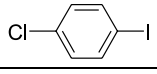
Scheme 1.

In connection with our work about the use of oxime-derived palladacycles[17] as very active precatalyst in cross-coupling reactions, such as Heck,[18] Suzuki,[19] Sonogashira,[20] and acylation of alkynes[21] in organic and aqueous solvents, we report here the scope of this type of catalysts in the chemoselective synthesis of cinnamaldehyde derivatives and ethyl 3-arylpropanoates[22] by arylation of acrolein diethyl acetal.



Scheme 2.

Table 1. Synthesis of cinnamaldehyde derivatives[a]

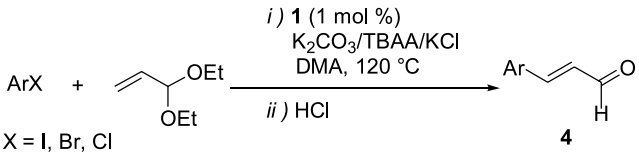
Entry	ArX	Mol% Pd	*t* (h)	Base	Solvent	*T* (°C)	Conv. (%)[b]	Ratio (**2**/**3**)[c]
1		1	8	K_2CO_3/TBAA	DMA	90	82	1:0
2		1	6	K_2CO_3/TBAA	DMA/H_2O[d]	90	99	4.9:1
3		1	14	K_2CO_3/TBAH	DMA/H_2O[d]	90	86	16.2:1
4		2	14	K_2CO_3/TBAA	DMA/H_2O[d]	120	0	—
5		1	3	K_2CO_3/TBAA/KCl	DMA/H_2O[d]	120	99	2.8:1
6		1	3	K_2CO_3/TBAA/KCl	DMA	120	99	10:1 (79)
7		1	2	K_2CO_3/TBAA/KCl	DMA	120	99	1:0 (82)
8		0.1	22	K_2CO_3/TBAA/KCl	DMA	120	99	1:0
9		1	2	K_2CO_3/TBAA/KCl[e]	DMA	120	99	10:1

Reaction conditions study.
[a] Reaction conditions: aryl halide (1 mmol), acrolein diethyl acetal (1.5 mmol), K_2CO_3 (1.5 mmol), ammonium salt (2 mmol), KCl (when added, 1 mmol), palladacycle **1** and solvent (5 mL).
[b] Determined by GLC using decane as internal standard.
[c] Determined by GLC. In brackets isolated yield of **4** after hydrolysis and flash chromatography.
[d] Volume ratio 4:1.
[e] Only 1 mmol of TBAA.

2. Results and discussion

2.1. Synthesis of cinnamaldehyde derivatives

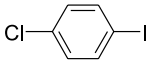
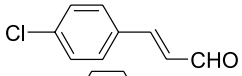
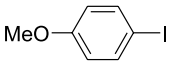
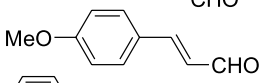
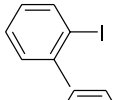
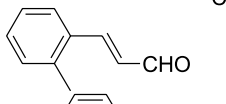
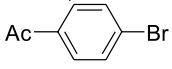
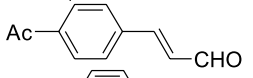
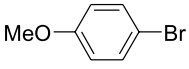
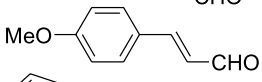
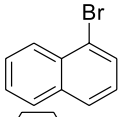
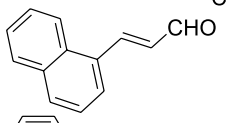
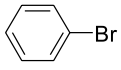
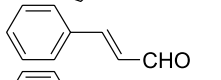
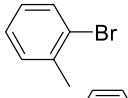
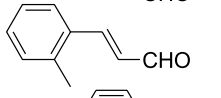
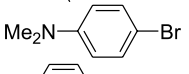
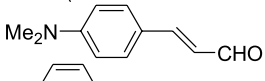
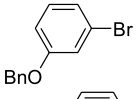
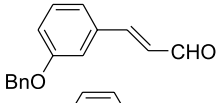
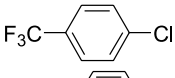
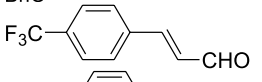
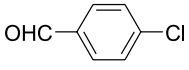
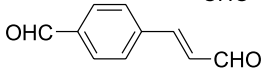
Initial studies concerning the reaction conditions for the arylation of acrolein diethyl acetal (1.5 equiv) catalyzed by 4-hydroxyacetophenone oxime-derived palladacycle **1** were performed with 1 equiv of the activated 4-chloroiodobenzene and the deactivated 4-methoxyiodobenzene (Scheme 2 and Table 1). The reactions carried out with 4-chloroiodobenzene using K_2CO_3 (1.5 equiv) and tetra-*n*-butylammonium acetate (TBAA) (2 equiv) as bases at 90 °C in *N*,*N*-dimethylacetamide (DMA) or in aqueous DMA, gave complete selectivity in neat DMA although, the reaction was faster in aqueous DMA (Table 1, entries 1 and 2). The use of tetra-*n*-butylammonium hydroxide (TBAH) instead of acetate gave a 16:1 ratio of compounds **2** and **3** in longer reaction times (Table 1, entry 3). In the case of 4-methoxyiodobenzene the reaction failed and KCl has to be added and the temperature increased at 120 °C in the absence of water in order to get a 10:1 ratio of compounds **2**/**3** (Table 1, compare entries 4–6). These reaction conditions were applied to the coupling with 4-chloroiodobenzene, which could be performed with total chemoselectivity in a shorter time (Table 1, entry 7). When lower palladium loading (0.1 mol%) was used higher reaction rate was observed for completion (Table 1, entry 8). When the amount of TBAA was decreased from 2 to 1 equiv the reaction also proceeded but with lower selectivity (Table 1, entry 9). On the other hand, attempts to perform the arylation of acrolein with *p*-cloroiodobenzene under this reaction conditions either at room temperature or at 80 °C failed.



Scheme 3.

For the synthesis of different cinnamaldehyde derivatives **4** the hydrolysis of compounds **2** was conducted in situ by addition of hydrochloric acid to the reaction mixture after arylation of acrolein diethyl acetal with aryl iodides, bromides and chlorides (Scheme 3 and Table 2). Under the best reaction conditions [**1** (0.5 mol%), TBAA, K_2CO_3, KCl, DMA at 120 °C] the arylation took place in short reaction times with good yields, only failing with

Table 2. Synthesis of cinnamaldehyde derivatives[a]

Entry	ArX	*t* (h)	No.	Product	Yield (%)[b]
1		2	**4a**		82
2		3	**4b**		79
3		3	**4c**		82
4		3	**4d**		59
5		3	**4b**		75
6		2	**4e**		80
7		2	**4f**		81
8		5	**4c**		71
9		3	**4g**		73
10		3	**4h**		67
11		14	**4i**		71[c]
12		14	**4j**		31[c]

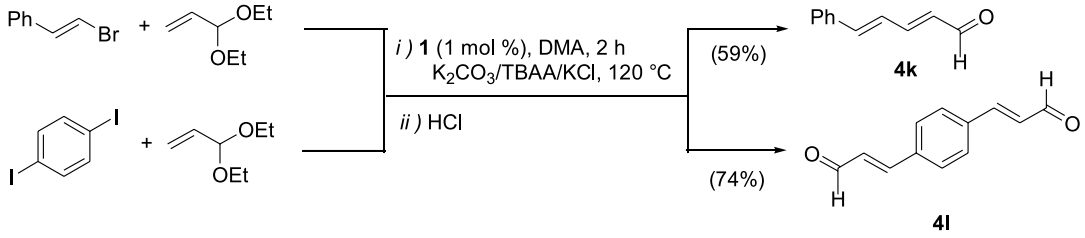
[a] Reaction conditions: aryl halide (1 mmol), acrolein diethyl acetal (1.5 mmol), K_2CO_3 (1.5 mmol), TBAA (2 mmol), palladacycle **1** (1 mol% Pd), DMAc (4 mL) and 120 °C.
[b] Isolated yields after hydrolysis and flash chromatography.
[c] Reaction performed in a 15 mL Ace pressure tube.

deactivated aryl chlorides. Ethyl 3-arylpropanoates were obtained in low yields ranging from 5 to 15%. Cinnamaldehydes **4** bearing electron-donating and -withdrawing groups were obtained in good yields. Some selected examples are *p*-(dimethylamino)cinnamaldehyde (**4g**), which is an important unit for nonlinear optics,[13] and 3-benzyloxycinnamaldehyde (**4h**), which has shown the most potent inhibitory activity against cyclin dependent kinases, specially cyclin D1-CDK4.[6b] The starting 3-(benzyloxy)phenyl bromide, used for the synthesis of the last compound **4h**, was prepared in 71% yield by benzylation of 3-bromophenol with benzyl bromide and K_2CO_3 under acetone reflux for 1 day. The reaction conditions with complex **1** are rather similar than the described conditions with $Pd(OAc)_2$ by Cacchi et al.[13] In the case of $Pd(OAc)_2$ the arylation took place with 3 mol% of catalyst in 1.5–15 h in 70–88% yields at 90 °C in DMF with 3 equiv of acrolein diethyl acetal, whereas with complex **1** this process needed lower catalyst loading, 1 mol% of Pd, at 120 °C in DMA and occurred in general in lower rates (2–5 h).

The coupling with (*E*)-2-phenylvinyl bromide gave stereoselectively the (2*E*,4*E*)-dienic aldehyde **4k** in 59% yield (Scheme 4). However, for the synthesis of the unsaturated dialdehydes the *p*-diiodobenzene gave compound **4l** after 2 h in 74% yield and the *ortho*-derivative afforded an intractable mixture of compounds. The reaction of 4-metoxyiodobenzene with acrolein diethyl acetal under microwave irradiation at 120 W and 120 °C during 10 min gave a mixture of products, mainly the ethyl 3-(4-methoxyphenyl)propanoate. In the case of 4-methoxybromobenzene no reaction was observed.

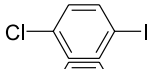
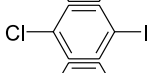
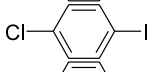
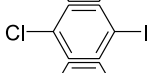
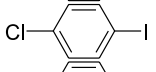
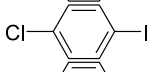
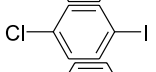
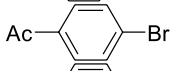
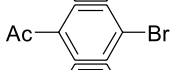
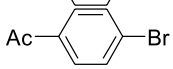
2.2. Synthesis of ethyl 3-arylpropanoates

Initial attempts to perform the preparation of ethyl 3-arylpropanoates were carried out by using 4-chloroiodobenzene and acrolein diethyl acetal (1.5 equiv) with complex **1** (0.1 mol% of Pd) as catalyst and (dicyclohexyl)-methylamine[23] as base (Table 3). When this coupling was performed in DMA as solvent, the reaction has to be heated at 120 °C (Table 3, entries 1 and 2). The reaction can also be carried out at 90 °C in a mixture of DMA/H_2O (4:1), but in neat water the arylation failed (Table 3, entries 3 and 4). When tri-*n*-butylamine was used instead of (dicyclohexyl)methylamine the reaction time increased from 4 to 7 h with a lower yield (Table 3, compare entries 3 and 5). The use of K_2CO_3 and TBAB as



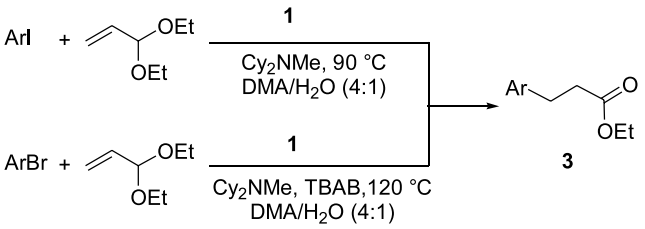
Scheme 4.

Table 3. Synthesis of ethyl 3-arylpropanoates[a]

Entry	ArX	Mol% Pd	*t* (h)	Base	Additive	Solvent	*T* (°C)	Conv.(%)[b]
1		0.1	8	Cy_2NMe	—	DMA	120	99
2		0.1	21	Cy_2NMe	—	DMA	90	0
3		0.1	4	Cy_2NMe	—	DMA/H_2O[c]	90	99 (79)
4		0.1	8	Cy_2NMe	—	H_2O	90	0
5		0.1	7	Bu_3N	—	DMA/H_2O[c]	90	87
6		1	4	K_2CO_3	TBAB	DMA/H_2O[c]	90	92
7		0.1	6	K_2CO_3	TBAB	DMA/H_2O[c]	90	0
8		0.1	3	Cy_2NMe	TBAB	DMA/H_2O[c]	90	0
9		0.1	3	Cy_2NMe	TBAB	DMA/H_2O[c]	120	99 (76)
10		0.1	3	Cy_2NMe	—	DMA/H_2O[c]	120	86

Reaction conditions study.
[a] Reaction conditions: aryl halide (1 mmol), acrolein diethyl acetal (1.5 mmol), base (1.5 mmol), additive (1 mmol), palladacycle **1** (see Table) and solvent (5 mL).
[b] Determined by GLC using decane as internal standard. In brackets isolated yield after flash chromatography.
[c] Volume ratio 4:1.

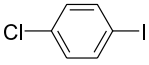
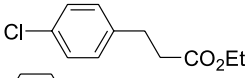
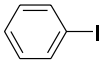
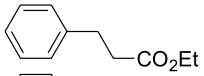
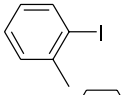
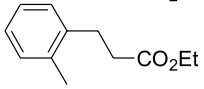
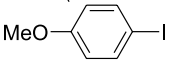
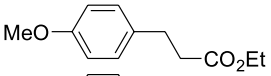
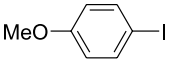
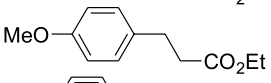
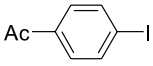
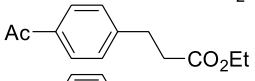
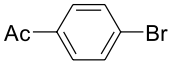
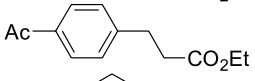
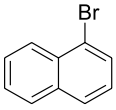
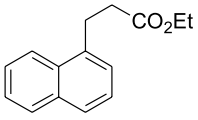
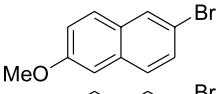
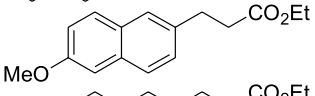
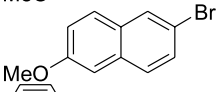
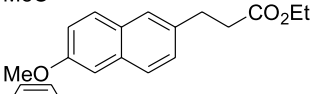
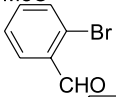
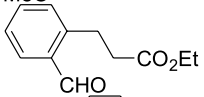
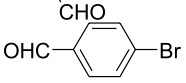
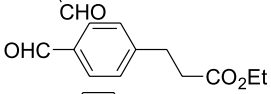
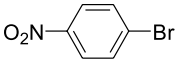
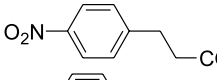
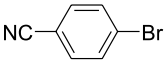
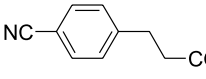
additive in aqueous DMA needed a higher catalyst loading (1 mol% of Pd) (Table 3, entries 6 and 7). Just a simple change in the additive (TBAB instead of TBAA) reversed completely the selectivity of the reaction (compare Table 1, entry 2 and Table 3, entry 6). The best conditions for the aryl iodide [Cy_2NMe, DMA/H_2O (4:1)] were applied to the reaction of acrolein diethyl acetal and 4-bromoacetophenone, revealing that in this case TBAB as additive and 120 °C have to be used in order to get good conversion in short times (Table 3, entries 8–10).



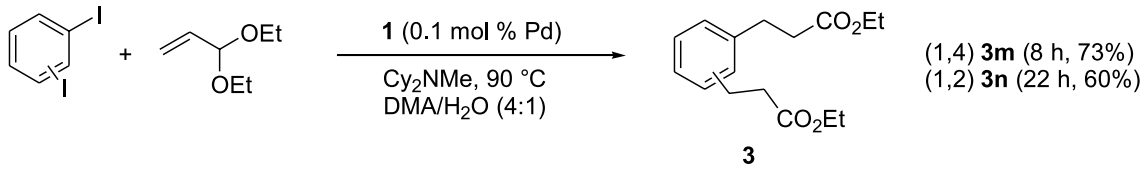
Scheme 5.

The synthesis of a variety of ethyl 3-arylpropanoates **3** can be performed with activated and deactivated aryl iodides and bromides bearing different functional groups, even at the *ortho*-position, by using Cy_2NMe as base in aqueous DMA (Scheme 5 and Table 4). For aryl iodides the arylation was performed at 90 °C and for bromides at 120 °C in the presence of TBAB. Deactivated aryl bromides, such as 4-methoxybromobenzene showed very low reactivity. In general, the reactions can be performed with lower loading of palladium than in the case of $Pd(OAc)_2$.[16] Thus, by using complex **1** between 0.1 and 1 mol% of Pd was used and the couplings took place in 2–8 h in 69–87% yield. For

Table 4. Synthesis of ethyl 3-arylpropanoates[a]

Entry	ArX	Mol% Pd	*t* (h)	No.	Product	Yield (%)[b]
1		0.1	4	**3a**		79
2		0.1	4	**3b**		79
3		0.1	6	**3c**		87
4		0.1	8	**3e**		69
5		0.1	10 min[c]	**3e**		71[d]
6		1.2×10^{-2}	23	**3f**		49
7		0.1	3	**3f**		76
8		1	5	**3g**		71
9		1	5	**3h**		53
10		1	10 min[e]	**3h**		76[d]
11		1	3	**3i**		83
12		0.1	3	**3j**		81
13		0.1	2	**3k**		86
14		0.1	3	**3l**		86

[a] Reaction conditions: aryl halide (1 mmol), acrolein diethyl acetal (1.5 mmol), Cy_2NMe (1.5 mmol), TBAB (1 mmol, only for aryl bromides), palladacycle **1** (see Table), DMA (4 mL) and H_2O (1 mL) at 90 °C for aryl iodides and 120 °C for aryl bromides.
[b] Isolated yields after flash chromatography.
[c] The reaction was performed under microwave irradiation conditions (120 W, 90 °C) at 0.5 mmol scale.
[d] Conversion determined by GC based on the aryl halide using decane at internal standard.
[e] The reaction was performed under microwave irradiation conditions (120 W, 120 °C) at 0.5 mmol scale.



Scheme 6.

comparison, in the case of $Pd(OAc)_2$ 3 mol% of Pd was used to afford similar couplings in 1–29 h and in 42–92% yield. This type of arylation can be also performed in 10 min under microwave irradiation at 120 W and 90 or 120 °C for compounds **3e** or **3h**, respectively (Table 4, entries 5 and 10). However, so far this type of arylation could not be performed with aryl chlorides under the essayed reaction conditions.

This Heck reaction with acrolein diethyl acetal were essayed with 1,4- and 1,2-diiodobenzene and the corresponding diesters **3m** and **3n** were obtained in good yields after 8 and 22 h, respectively (Scheme 6). Rather low loading of Pd (0.1 mol%) was used in comparison with the same couplings using $Pd(OAc)_2$,[6] which needed a higher catalysts loading (6 mol%) to afford compounds **3m** and **3l** in similar yields (77 and 61%) and reaction rates (3 and 24 h).

3. Conclusion

In conclusion, we have found that the arylation of acrolein diethyl acetal can be performed with lower loading of acrolein and catalyst using the 4-hydroxyacetophenone oxime-derived palladacycle **1** instead of $Pd(OAc)_2$ by choosing the appropriate base, solvent, temperature and additive. Cinnamaldehyde derivatives can be prepared by using aryl iodides, bromides and activated chlorides, whereas ethyl 3-arylpropanoates have been prepared using iodides and bromides under thermal or microwave irradiation conditions.

4. Experimental

4.1. General

The reagents and solvents were obtained from commercial sources and were generally used without further purification. Flash chromatography was performed on silica gel 60 (0.040–0.063 mm, Merck). Thin-layer chromatography was perfomed on Polygram® SIL G/UV_{254} plates. Melting point were determined on a Reichert Thermovar apparatus. Gas chromatographic analyses were performed on a HP-6890 instrument equipped with a WCOT HP-1 fused silica capillary column. IR data were collected on a Nicolet Impact-400D-FT spectrophotometer in cm^{-1}. ^1H NMR spectra were recorded on Bruker AC-300 (300 MHz). Chemical shifts are reported in ppm using tetramethylsilane (TMS, 0.00 ppm) as internal standards. ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ as the internal reference. EI-MS were measured on a mass selective detector G2579A from Agilent Technologies 5973N in *m/z* (rel int. in % of base peak). HRMS were performed on a Finningan MAT95S apparatus. Elemental analysis were carried out in a Carlo Erba EA 1108 (CHNS–O) by the corresponding services at the University of Alicante. The catalysts were weighed up in an electronic microscale (Sartorius, XM1000P) with precision of 1 μg. Microwave reactions were performed with a CEM discover synthesis unit in glass vessels (10 mL) sealed with a septum under magnetic stirring.

4.2. General procedure for the synthesis of cinnamaldehyde derivatives (4)

A suspension of aryl halide (1 mmol), acrolein diethyl acetal (229 μL, 1.5 mmol), potassium carbonate (207 mg, 1.5 mmol), tetra-*n*-butylammonium acetate (602 mg, 2 mmol), potassium chloride (75 mg, 1 mmol), **1** (2.918 mg, 0.005 mmol, 1 mol% Pd) and *N*,*N*-dimethylacetamide (4 mL) was stirred at 120 °C (bath temperature) in air, and the reaction progress was analyzed by GLC. After the reaction was completed, it was cooled and an aqueous solution of 2 M HCl (10 mL) was added slowly and the mixture was stirred at room temperature for 10 min. Then the reaction crude was poured into ethyl acetate (20 mL) and washed successively with 2 M HCl (20 mL) and H_2O (2×20 mL). The organic layer was dried over Na_2SO_4, evaporated (15 mmHg) and the resulting residue purified by flash chromatography to provide compounds **4**.

The compounds cinnamaldehyde, *p*-(dimethylamino)-cinnamaldehyde, *p*-chlorocinnamaldehyde, *p*-methoxycinnamaldehyde and *o*-methyl-cinnamaldehyde are commercially available and *p*-acetylcinnamaldehyde,[13] *m*-benzyloxycinnamaldehyde,[6b] *p*-(trifluoromethyl)cinnamaldehyde,[25] *p*-formylcinnamaldehyde,[13] 5-phenyl-2,4-pentadienal[26] and 1,4-phenylenediacrylaldehyde[27] have been previously reported and were characterized by comparison with their reported data. The characterization data of compounds previously not reported is given below.

4.2.1. 3-(1-Naphthyl)acrolein. R_f 0.20 (hexane–EtOAc: 9/1); mp 49–51 °C; IR (KBr): ν=2826, 1679 cm^{-1}; ^1H NMR: δ=6.76 (dd, 1H, *J*=15.8, 7.8 Hz, C*H*CHO), 7.42–7.60 (m, 3H, ArH), 7.72 (d, 1H, *J*=7.2 Hz, ArH), 7.84–7.90 (m, 2H, ArH), 8.11 (d, 1H, *J*=8.3 Hz, ArH), 8.22 (d, 1H, *J*=15.8 Hz, C*H*CHCHO), 9.78 (d, 1H, *J*=7.8 Hz, CHO); ^{13}C NMR: δ=122.7, 125.4, 125.6, 126.3, 127.2, 128.9, 130.7, 130.8, 131.1, 131.6, 133.7, 149.2, 193.4, 197.3; MS: *m/z* (rel int.) 182 (M^+, 53), 181 (M^+-1, 100), 165 (14), 154 (24), 153 (95), 152 (77), 151 (30), 150 (17), 128 (15), 127 (10), 126 (14), 77 (20), 76 (39), 75 (16), 63 (22), 62 (11), 51 (22), 50 (17). Anal. Calcd for $C_{13}H_{10}O$: C 85.69, H 5.53; found: C 84.99, H 5.51.

4.3. General procedure for the synthesis of ethyl 3-arylpropanoates (3)

A solution of aryl halide (1 mmol), acrolein diethyl acetal (229 μL, 1.5 mmol), dicyclohexylmethylamine (321 μL, 1.5 mmol), tetra-*n*-butylammonium bromide (322 mg, 1 mmol, only for aryl bromides), **1** (0.1–1 mol% Pd) in *N*,*N*-dimethylacetamide (4 mL) and water (1 mL) was stirred at 90 °C or at 120 °C (bath temperature) for aryl iodides or aryl bromides respectively, in air, and the reaction progress was analyzed by GLC. After the reaction was completed, the resulting solution was cooled, poured into ethyl acetate (20 mL) and washed successively with 2 M HCl (2×20 mL) and H_2O (20 mL). The organic layer was dried over Na_2SO_4, evaporated (15 mmHg) and the residue was purified by flash chromatography to afford products **3**.

The compounds ethyl 3-(*p*-chlorophenyl)propanoate,[28] ethyl 3-phenylpropanoate,[29] ethyl 3-(*o*-tolyl)propanoate,[30] ethyl 3-(*p*-methoxyphenyl)propanoate,[29] ethyl 3-(*p*-acetylphenyl)propanoate,[29] ethyl 3-(1-naphtyl)propanoate,[31] ethyl 3-(6-methoxy-2-naphtyl)propanoate,[28] ethyl 3-(*p*-cyanophenyl)propanoate,[32] ethyl 3-[4-(2-ethoxycarbonylethyl)-phenyl]propanoate,[16] and ethyl 3-[2-(2-ethoxycarbonylethyl)phenyl]-propanoate[16] have been previously reported and were characterized by comparison with their reported data. Data of not described compounds are given below.

4.3.1. Ethyl 3-(2-formylphenyl)propanoate. R_f 0.27 (hexane–EtOAc: 9/1); oil; IR (film): ν=2740, 1731, 1694 cm^{-1}; ^1H NMR: δ=1.22 (t, 3H, J=7.2 Hz, CH_3), 2.64 (t, 2H, J=7.6 Hz, $ArCH_2CH_2$), 3.36 (t, 2H, J=7.6 Hz, $ArCH_2CH_2$), 4.11 (c, 2H, J=7.1 Hz, CH_2CH_3), 7.33 (d, 1H, J=7.5 Hz, ArH), 7.34–7.54 (m, 2H, ArH), 7.82 (dd, 1H, J=7.5, 1.4 Hz, ArH), 10.22 (s, 1H, CHO); ^{13}C NMR: δ=4.2, 28.0, 35.5, 60.4, 127.0, 131.2, 133.4, 133.8, 142.9, 172.6, 192.7; MS: *m*/*z* (rel int.) 206 (M^+, 5), 188 (19), 162 (22), 161 (27), 160 (38), 134 (10), 133 (58), 132 (91), 131 (43), 118 (21), 115 (28), 105 (72), 104 (100), 103 (36), 91 (60), 79 (40), 78 (33), 77 (68), 66 (18), 65 (33), 63 (17), 51 (50); HRMS: calcd for $C_{12}H_{14}O_3$: 206.0943; found: 206.0944.

4.3.2. Ethyl 3-(4-formylphenyl)propanoate. R_f 0.20 (hexane–EtOAc: 9/1); oil; IR (KBr): ν=2736, 1732, 1702 cm^{-1}; ^1H NMR: δ=1.23 (t, 3H, J=7.1 Hz, CH_3), 2.66 (t, 2H, J=7.6 Hz, $ArCH_2CH_2$), 3.04 (t, 2H, J=7.6 Hz, $ArCH_2CH_2$), 4.13 (c, 2H, J=7.1 Hz, CH_2CH_3), 7.38 (d, 2H, J=8.0 Hz, ArH), 7.81 (d, 2H, J=8.0 Hz, ArH); ^{13}C NMR: δ=14.2, 31.0, 35.2, 60.6, 129.0, 130.0, 134.8, 147.9, 172.4, 191.9; MS: *m*/*z* (rel int.) 206 (M^+, 33), 177 (15), 161 (13), 135 (36), 133 (31), 132 (63), 131 (28), 119 (19), 107 (13), 105 (28), 104 (20), 103 (21), 91 (31), 79 (24), 78 (18), 77 (34), 76 (12), 66 (12), 65 (15), 63 (12), 60 (29), 51 (32); HRMS: calcd for $C_{12}H_{14}O_3$: 206.0943; found: 206.0942.

4.3.3. Ethyl 3-(4-nitrophenyl)propanoate. R_f 0.17 (hexane–EtOAc: 9/1); oil; IR (film): ν=1732, 1519, 1346 cm^{-1}; ^1H NMR: δ=1.24 (t, 3H, J=7.1 Hz, CH_3), 2.70 (t, 2H, J=7.5 Hz, $ArCH_2CH_2$), 3.08 (t, 2H, J=7.5 Hz, $ArCH_2CH_2$), 4.14 (c, 2H, J=7.1 Hz, CH_2CH_3), 7.40 (d, 2H, J=8.5 Hz, ArH) 8.15 (d, 2H, J=8.5 Hz, ArH); ^{13}C NMR: δ=14.1, 30.5, 34.9, 60.5, 123.6, 129.2, 146.5, 148.3, 172.0; MS: *m*/*z* (rel int.) 223 (M^+, 29), 195 (M^+-28, 9), 178 (M^+-45, 23), 153 (15), 152 (31), 150 (37), 149 (100), 136 (18), 133 (10), 119 (16), 103 (30), 91 (23), 78 (35), 77 (35), 63 (17); HRMS: calcd for $C_{11}H_{13}NO_4$: 223.0845; found: 223.0842.

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