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Highly stereoselective palladium-catalyzed coupling reactions of captodative olefins acetylvinyl arenecarboxylates [1]

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Abstract

The palladium-catalyzed reaction of the captodative olefin 3-(*p*-nitrobenzoyloxy)-3-buten-2-one (**1a**) with aryl and vinyl halides gave coupled products 4-aryl- and 4-vinyl-3-(*p*-nitrobenzoyloxy)-3-buten-2-ones, **4** and **6** respectively, with high *Z* stereoselection. $(Ph_3P)_2PdCl_2$ also catalyzed cross-coupling alkylation, phenylation and vinylation with trialkylorganostannanes and bromo olefin (*Z*)-4-bromo-3-(*p*-nitrobenzoyloxy)-3-buten-2-one (**2**), providing the corresponding trisubstituted alkenes. For the preparation of *n*-butyl substituted derivative (*Z*)-3-(*p*-nitrobenzoyloxy)-3-octen-2-one (**8b**), the transmetallation with *n*-BuZnCl was a more efficient method. Retention of the *Z* configuration of **2** was in all cases maintained.

Keywords: Palladium; Tin; Zinc; Coupling reactions; Olefins; Arylation; Organostannanes

1. Introduction

Palladium(0)-catalyzed arylation and vinylation of olefins with aryl- or vinyl halides, also known as the Heck reaction, has become a very useful method in organic synthesis [1]. The Stille reaction is another versatile carbon–carbon bond forming reaction through the palladium(0)-catalyzed cross-coupling of trialkylorganostannanes with organic halides or triflates [2]. The regioselectivity of the arylative coupling with monosubstituted olefins seems to be controlled by steric and π-bond polarization factors. With olefins bearing electron-withdrawing groups, insertion occurs on the unsubstituted carbon with high trans-stereoselectivity. Whereas with olefins bearing electron-donor groups, such as alkoxy, mixtures of regioisomers [3] with low stereoselectivity [4] may be obtained.

Captodative olefins have attracted a great interest for evaluating the opposite electronic effect of the substituents on the polarizability of the double bond, particularly in Diels–Alder reactions [5]. Few reports have been devoted to the Heck reaction in this kind of olefins [6]. For example, Carlström and Frejd [7] have shown that palladium(0)-catalyzed arylation of 2-aminoacrylates gave, mainly, the β-arylated product with *Z* configuration. Previously, we studied the captodative olefins 1-acetylvinyl arenecarboxylates (**1**) in Diels–Alder [8] and 1,3-dipolar [9] cycloadditions, and they proved to be useful synthons in natural product synthesis [10].

Herein, and as a part of our interest in the stereoselective β-functionalization of these olefins [11], we describe a study of the selectivity in the reaction of arylation and vinylation of olefin **1a** under Heck conditions. We have also evaluated an alternative method to functionalize these molecules with alkyl, aryl and vinyl groups via the palladium(0)-catalyzed cross-coupling process with trialkylorganostannanes and alkylzinc halides, using bromo olefin **2** as the substrate.

2. Results and discussion

2.1. Palladium(0)-catalyzed arylation and vinylation of 1a

For this study we decided to use olefin **1a**, since it proved to be the most stable under thermal and Lewis

[1] Dedicated to the memory of Professor A. Héber Muñoz.
* Corresponding authors.

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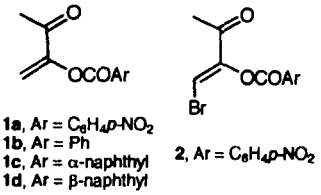
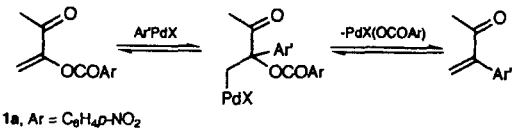




Scheme 1.

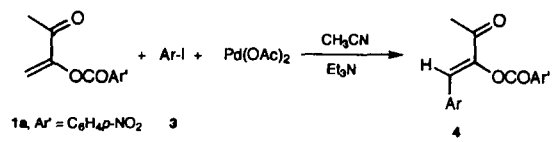
acids conditions, and to be an efficient starting material for the β-functionalization of the double bond [11]. The palladium(0)-catalyzed arylation trials of **1a** are summarized in Table 1. This shows a low reactivity of ortho-substituted aryl iodides **3f** and **3g**, since only starting material was recovered. Moreover, compound **1a** decomposed after heating to 90°C. Compounds **4a–4e** were obtained in moderate to low yields. This was probably due to the low reactivity of the olefin with the aryl halide and to the long reaction times. In the case of **3d**, a steric effect by the ortho substituent could be involved [12], as a similar trend was observed for the *o*-anisyl compound **3g**.

Triarylphosphines have proved to be efficient additives in improving the Heck reactions [13]. Indeed, when the preparation of olefin **4c** was carried out in the presence of triphenylphosphine, the yield was considerably enhanced (Table 1, entry 10). Less remarkable improvement was observed in the arylation with **3b**, compared with that experiment made in the absence of phosphine, since olefin **4b** was isolated in 60% yield (Table 1, entries 2 and 9).

The ^{1}H NMR analysis of the crude mixtures of olefins **4a–4e** showed only the presence of one isomer, which corresponded to the *Z* geometry, as established by NOE experiments. Double irradiation of the singlet of the enone methyl group induced an enhancement of the signal of the vinylic proton. Conversely, when the latter was irradiated, the methyl group singlet was increased.

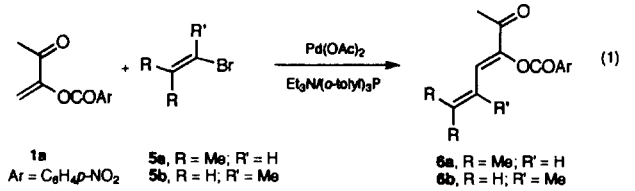
A feasible electronic control by the electron-donor *p*-nitrobenzoyloxy group (OPNB) of **1a** could favor the formation of the regioisomeric α-arylated product [14], which would be obtained from a possible α-insertion of the aryl ring and followed by a β-elimination of the σ-palladium complex with the OPNB group [15] (Scheme 1). However, this product was not detected by NMR from the crude reaction mixtures. Probably, steric

Table 1
Palladium arylation of olefin **1a** in the presence of aryl iodides **3a–3e**



Entry	3 (Ar)	$Pd(OAc)_2$ (mol eq.)	Et_3N (mol eq.)	Ph_3P (mol eq.)	*T* (°C)	*t* (h)	**4** m.p. (°C)	Yield [a] (%)
1	**3a** (Ph)	0.031	1.93	—	50	48	174–175	64
2	**3b** (*p*-tolyl)	0.031	1.93	—	50	48	145–146	54
3	**3c** (*p*-anisyl)	0.031	1.93	—	65	121	158–159	31
4	**3d** (*o*-tolyl)	0.031	1.93	—	65	115	108–109	27
5	**3e** (α-naphthyl)	0.031	1.93	—	65	50	110–111	48
6	**3f** (*o*-anilyl)	0.031	1.93	—	50	48	—	— [b]
7	**3g** (*o*-anisyl)	0.035	2.26	—	70	64	—	— [b]
8	**3g** (*o*-anisyl)	0.035	2.26	—	90	64	—	— [c]
9	**3b** (*p*-tolyl)	0.031	1.93	1.01	50	48	145–146	60
10	**3c** (*p*-anisyl)	0.031	1.93	1.01	65	121	158–159	60

[a] After column chromatography and recrystallization. [b] Starting material was recovered. [c] No traces of **4** and decomposition of **1a**.



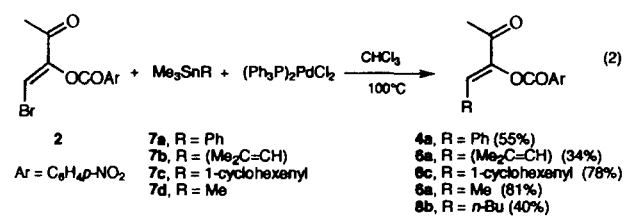
factors control the insertion into the least substituted carbon of the double bond [16].

The vinylation of **1a** catalyzed by Pd(0) with vinyl bromides **5a** and **5b** took place in low yields to give captodative dienes **6a** and **6b** in 18% and 32% yield respectively (Eq. (1)). In this reaction, tri-*o*-tolylphosphine was used as the additive, in order to improve the process [17]. The lesser reactivity of the aryl and vinyl bromides, as compared with the corresponding iodides, has been previously well documented [1,3,6a,18]. These dienes were relatively unstable, which is probably the main reason for the decrease of the yields, but they could be characterized by spectroscopy. This vinylation was also stereoselective, since only the *Z* isomer could be detected by ^{1}H NMR of the crude mixtures.

The high *Z* stereoselectivity observed in these reactions could be explained on the basis of the mechanism proposed for the Heck reaction [19]. Both processes, the insertion of the palladium(II)–π-olefin complex and the β-hydride elimination, occur in a stereospecific syn manner [20]. The latter is reversible and, therefore, it should depend on the stability of the newly formed olefin. Indeed, when monosubstituted olefins suffer a Heck arylation and vinylation, the stereoisomer obtained is usually the most stable [1c,6a]. Also likely, is that the *Z*-geometric preference obtained in our case could be associated not only with a steric demand [6c], but also with an electronic factor of the conjugated enone. The s-cis and/or s-trans planar conformation of the β-conjugated-π-enone system of these trisubstituted olefins appears to be more stable when the acetyl group and the β substituent, aryl or vinyl group, are on opposite sides of the double bond [11].

2.2. Organotin and organozinc palladium(II)-catalyzed cross-coupling reactions of olefin 2

We have also evaluated the Stille method [2] as an alternative procedure to functionalize olefins **1**. In this



case, the cross-coupling process of trialkylorganostannanes **7** with bromo olefin **2** [21], in the presence of

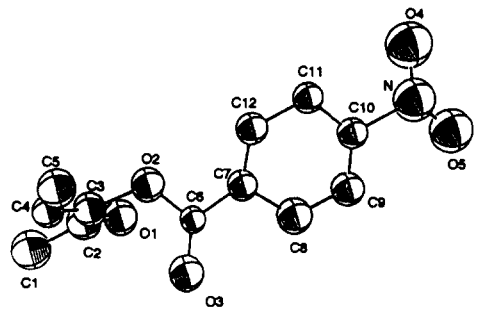


Fig. 1. Perspective view of the X-ray crystal structure of **8a**. Hydrogen atoms are omitted for clarity.

catalytic amounts of the Pd(II) complex, yielded the corresponding trisubstituted alkenes (Eq. (2)). The phenylation was carried out by heating to 100°C in $CHCl_3$ for 12 h in a sealed tube, in the presence of 5 mol% of $(Ph_3P)_2PdCl_2$, to give 55% of **4a**. Trimethylphenyltin (**7a**) had to be used because the tributyltin derivative failed to give the desired product. Trimethyltin reagents, where not commercially available, were prepared by reaction between the lithium reagent and trimethyltin chloride in THF [22]. Compound **4a** presented the same spectroscopic properties as those obtained by direct phenylation under the Heck conditions, thereby showing the same *Z* configuration.

Vinyl derivatives **6a** and **6c** were prepared from **2** by treatment of the corresponding trimethylvinyltin **7b** or **7c**, under conditions analogous with **4a** (Eq. (2)) [2a].

Successful methylation of **2** was possible through a cross-coupling reaction with **7d**, to give **8a** in good

Table 2
Crystallographic data for **8a**

Formula	$C_{12}H_{11}NO_5$
Mw	249.33
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a (Å)	8.2050(8)
b (Å)	11.629(2)
c (Å)	25.400(4)
V (Å^3)	2423.4(3)
λ (Å)	0.71073
Z	8
Crystal dimensions (mm^3)	0.04×0.11×0.12
μ (cm^{-1})	1.01
$D_{calcd.}$ (g cm^{-3})	1.366
Temperature (°C)	25
2θ scan range (deg)	2–44
Scan type	ω
No. of reflections collected	1348
No. of unique reflections	1348
No. of unique observed reflections	525
R_f	0.0698
Rw_f	0.0717
Max. final shift/esd	< 0.01

Table 3
Atomic coordinates and equivalent isotropic displacement parameters (Å^2) (estimated standard deviations) for **8a**

Atom	x	y	z	B_{eq}
O(1)	0.376(2)	0.308(1)	0.6132(7)	6.0(5)
O(2)	0.521(2)	0.508(1)	0.5840(6)	4.8(4)
O(3)	0.711(2)	0.381(1)	0.5712(6)	5.2(4)
O(4)	0.399(3)	0.585(2)	0.3216(8)	9.0(6)
O(5)	0.586(3)	0.457(2)	0.3031(7)	7.9(6)
N	0.519(3)	0.523(2)	0.3318(9)	7.2(7)
C(1)	0.417(4)	0.323(3)	0.705(1)	7.5(9)
C(2)	0.427(4)	0.373(2)	0.649(1)	5.6(7)
C(3)	0.518(3)	0.484(2)	0.6404(9)	4.5(6)
C(4)	0.567(3)	0.553(2)	0.6749(8)	3.7(6)
C(5)	0.637(3)	0.665(2)	0.661(1)	4.9(7)
C(6)	0.611(3)	0.443(2)	0.5522(8)	2.9(5)
C(7)	0.576(3)	0.469(2)	0.5004(8)	3.8(6)
C(8)	0.645(3)	0.392(2)	0.4606(9)	5.2(7)
C(9)	0.624(3)	0.409(2)	0.4074(9)	4.6(7)
C(10)	0.547(3)	0.503(2)	0.3937(8)	3.7(6)
C(11)	0.472(3)	0.577(2)	0.4258(8)	3.7(6)
C(12)	0.503(3)	0.563(2)	0.4813(9)	4.1(6)

yield. However, the *n*-butyl derivative **8b** could not be obtained by this method: with the tetrabutyltin reagent the reaction failed, and with the trimethylorganostannane a selective transfer of a butyl group over a methyl one would not be possible. Thus, it had to be prepared by coupling of *n*-butylzinc chloride (**9**) (from *n*-BuLi + $ZnCl_2$) with **2** in THF at 0°C with the same catalyst [23], to give **8b** in 40% yield.

In order to improve the preparation of these compounds, the Negishi procedure was tried, which has proved to be very efficient in these insertion reactions [24]. Thus, when the Pd catalyst was prepared by treating $(Ph_3P)_2PdCl_2$ with $^iBu_2AlH$, and olefin **2** and the organozinc reagent (prepared from the corresponding organolithium and dried $ZnCl_2$) were added sequentially at 0°C, olefins **4a**, **8a** and **8b** were isolated.

Table 4
Selected interatomic distances (Å), bond angles (deg) and torsion angles (deg) (estimated standard deviations) of crystal structure **8a**

Bond distances			
O(1)–C(2)	1.26(3)	N–C(10)	1.60(3)
O(2)–C(3)	1.46(3)	C(1)–C(2)	1.54(4)
O(2)–C(6)	1.32(3)	C(2)–C(3)	1.50(4)
O(3)–C(6)	1.20(0)	C(3)–C(4)	1.26(3)
O(4)–N	1.25(3)	C(4)–C(5)	1.46(4)
O(5)–N	1.19(3)	C(6)–C(7)	1.38(3)
Bond angles			
O(1)–C(1)–C(2)	116(2)	O(4)–N–C(10)	113(2)
O(1)–C(2)–C(3)	125(2)	O(5)–N–C(10)	117(2)
O(2)–C(2)–C(3)	108(2)	N–C(10)–N(9)	116(2)
O(2)–C(3)–C(4)	124(2)	N–C(10)–C(11)	116(2)
O(2)–O(3)–C(6)	119(2)	C(1)–C(2)–C(3)	119(2)
O(2)–C(3)–C(6)	120(2)	C(2)–C(3)–C(4)	127(2)
O(2)–C(6)–C(7)	110(2)	C(3)–C(4)–C(5)	122(2)
O(3)–C(6)–C(7)	131(2)	C(6)–C(7)–C(8)	117(2)
O(4)–N–O(5)	127(2)		
Torsion angles			
O(2)–C(3)–C(2)–O(1)	5.44(4)	C(3)–O(2)–C(6)–C(7)	170.60(2)
O(2)–C(3)–C(2)–C(1)	175.76(2)	C(4)–C(3)–C(2)–O(1)	177.24(3)
O(4)–N–C(10)–C(9)	154.49(2)	C(4)–C(3)–C(2)–C(1)	−12.44(4)
O(4)–N–C(10)–C(11)	−17.57(3)	C(5)–C(4)–C(3)–O(2)	−2.11(4)
O(5)–N–C(10)–C(9)	−7.92(4)	C(5)–C(4)–C(3)–C(2)	−172.74(3)
O(5)–N–C(10)–C(11)	−179.98(2)	C(6)–O(2)–C(3)–C(4)	117.52(3)
C(3)–O(2)–C(6)–O(3)	−13.65(3)	C(6)–O(2)–C(3)–C(2)	−70.31(3)

Whereas compound **4a** was prepared in 54% yield, which is comparable with that provided by the Stille method, methyl derivative **8a** was obtained in lesser yield (62%). Nevertheless, in the case of compound **8b**, the yield was slightly increased to 50%.

2.3. Configuration of trisubstituted olefins 6a, 6b, 8a and 8b, and molecular structure of 8a

Considering that the stereochemistry of the vinyl bromide is retained during the Stille reaction [2], it could then be expected that the configuration of compounds **6a**, **6b**, **8a** and **8b** have the same *Z* configuration as its precursor **2**, as was established by NOE experiments in the case of **4a**. Indeed, a confirmation of this was provided by the X-ray structure of **8a** (Fig. 1). Crystallographic data are summarized in Table 2. Positional parameters are listed in Table 3; selected bond distances, bond angles and torsion angles are collected in Table 4. It is also interesting to notice the planar s-trans conformation of this olefin, which is further evidence of this conformational preference in these molecules, both in solution and in the crystalline form [11].

3. Conclusions

The arylative and vinylative Heck reaction of captodative olefin **1a** was highly stereoselective, giving functionalized olefins **4a–4e** and dienes **6a** and **6b** respectively. The palladium(0)-catalyzed cross-coupling of alkyl, phenyl and vinyl groups with **2**, using both the corresponding trialkylorganostannanes and the organozinc chlorides, proved to be efficient and alternative methods of preparing β-substituted captodative olefins.

4. Experimental section

4.1. General

^1H and ^{13}C NMR spectra were obtained on Varian Gemini-300 (300 MHz) and Gemini-200 (200 MHz) instruments, with TMS as the internal standard. HRMS was carried out on Fisons Instruments VG AutoSpec. Further analytical procedures were described elsewhere [10c].

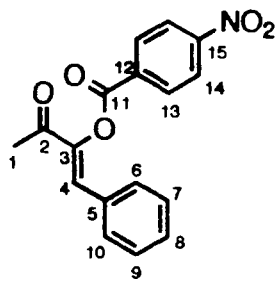
4.2. Preparation of olefins 4a–4e

Method A. Under an N_2 atmosphere, a mixture of 0.3 g (1.28 mmol) of **1a**, the corresponding aryl iodide **3**, 0.25 g (2.47 mmol) of Et_3N and 0.009 g (0.04 mmol) of $Pd(OAc)_2$ in dry CH_3CN (2.5 ml) was stirred and heated to 50°C or to 65°C until consumption of the starting material. The mixture was diluted with Et_2O (30 ml) and washed with cold saturated aqueous solutions of NH_4Cl (3 × 20 ml) and of KI (3 × 20 ml). The organic layer was filtered through Celite and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was purified by successive recrystallization from Et_2O–hexane (40:60) and EtOAc–MeOH (70:30).

Method B. Under an N_2 atmosphere, a mixture of 0.3 g (1.28 mmol) of **1a**, the corresponding aryl iodide **3**, 0.25 g (2.47 mmol) of Et_3N and 0.340 g (1.3 mmol) of Ph_3P and 0.009 g (0.04 mmol) of $Pd(OAc)_2$ in dry CH_3CN (2.5 ml) was stirred at 50°C or at 65°C until the consumption of the starting material. The mixture was diluted with Et_2O (30 ml) and washed with cold saturated aqueous solutions of NH_4Cl (3 × 20 ml) and KI (3 × 20 ml). The organic layer was filtered through Celite and dried (Na_2SO_4). The solvent was removed in vacuo and the residue purified by column chromatography (silica gel, hexane–EtOAc, 8:2).

4.2.1. (Z)-4-Phenyl-3-(p-nitrobenzoyloxy)-3-buten-2-one (4a)

Using the method A, **1a** was allowed to react with 0.265 g (1.3 mmol) of iodobenzene (**3a**) at 50°C for 48 h to obtain 0.26 g (64%) of **4a**, as a reddish powder. M.p. 174–175°C; IR (KBr) 1740, 1670, 1520, 1360, 1260, 1110, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.37 (s, 4H, PNB-H), 7.62 (m, 2H, H-6, H-10), 7.39–7.36 (m, 3H, H-7, H-9, H-8), 7.35 (s, 1H, H-4), 2.53 (s, 3H, CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.1 (C-2), 162.4 (C-9), 151.1 (C-15), 144.5 (C-3), 134.1 (C-10), 131.6 (C-5), 131.5 (2C, C-13), 130.5 (C-8), 130.2 (C-7, C-9), 129.2 (C-4), 129.0 (C-6, C-10), 123.9 (2C, C-14), 25.3 (C-1). Anal. Found: C, 65.77; H, 4.35. $C_{17}H_{13}NO_5$. Calc.: C, 65.59; H, 4.21%.



4.2.2. (Z)-3-(p-Nitrobenzoyloxy)-4-(p-tolyl)-3-buten-2-one (4b)

Using the method A, **1a** was allowed to react with 0.283 g (1.3 mmol) of 4-iodotoluene (**3b**) at 50°C for 48 h to obtain 0.228 g (54%) of **4b**, as a red powder.

Using the method B, **1a** was allowed to react with 0.283 g (1.3 mmol) of 4-iodotoluene (**3b**) at 50°C for 48 h to obtain 0.248 g (60%) of **4b**. M.p. 145–146°C; IR

(KBr) 1730, 1660, 1630, 1600, 1530, 1360, 1270, 1120, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.40 (s, 4H, PNB-H), 7.51 (m, 2H, H-6, H-10), 7.33 (s, 1H, H-4), 7.18 (m, 2H, H-7, H-9), 2.50 (s, 3H, CH_3CO), 2.35 (s, 3H, CH_3Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.1 (C-2), 162.4 (C-11), 151.0 (C-15), 143.9 (C-3), 141.2 (C-8), 134.2 (C-12), 131.5 (2C, C-13), 130.3 (C-7, C-9), 129.8 (C-6, C-10), 129.4 (C-5), 128.8 (C-4), 123.8 (2C, C-14), 25.3 (C-1), 21.5 ($ArCH_3$). Anal. Found: C, 66.22; H, 4.61. $C_{18}H_{15}NO_5$. Calc.: C, 66.46; H, 4.65%.

4.2.3. (Z)-4-(p-Anisyl)-3-(p-nitrobenzoyloxy)-3-buten-2-one (4c)

Using the method A, **1a** was allowed to react with 0.4 g (1.71 mmol) of 4-iodoanisole (**3c**) at 65°C for 121 h to obtain 0.18 g (31%) of **4c**, as a yellow powder.

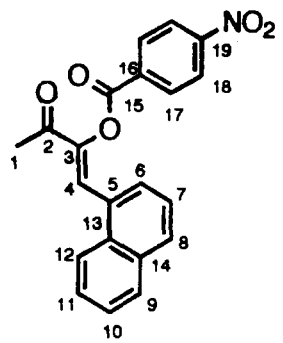
Using the method B, **1a** was allowed to react with 0.4 g (1.71 mmol) of 4-iodoanisole (**3c**) at 65°C for 121 h to obtain 0.261 g (60%) of **4c**. M.p. 158–159°C; IR (KBr) 1740, 1670, 1600, 1520, 1260, 1180, 1100, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.38 (s, 4H, PNB-H), 7.58 (m, 2H, H-6, H-10), 7.30 (s, 1H, H-4), 6.88 (m, 2H, H-7, H-9), 3.81 (s, 3H, CH_3O), 2.51 (s, 3H, CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.9 (C-2), 162.4 (C-11), 161.5 (C-8), 151.2 (C-15), 143.2 (C-3), 134.4 (C-12), 132.2 (C-6, C-10), 131.5 (2C, C-13), 129.0 (C-4), 124.3 (C-5), 123.9 (2C, C-14), 114.6 (C-7, C-9), 55.4 ($ArOCH_3$), 25.2 (C-1). Anal. Found: C, 63.26; H, 4.48. $C_{18}H_{15}NO_6$. Calc.: C, 63.34; H, 4.43%.

4.2.4. (Z)-3-(p-Nitrobenzoyloxy)-4-(o-tolyl)-3-buten-2-one (4d)

Using the method A, **1a** was allowed to react with 0.283 g (1.3 mmol) of 2-iodotoluene (**3d**) at 65°C for 115 h to obtain 0.114 g (27%) of **4d**, as a yellow powder. M.p. 108–109°C; IR (KBr) 1730, 1670, 1630, 1600, 1530, 1360, 1275, 1120, 800, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.3 (m, 4H, PNB-H), 7.57 (s, 1H, H-4), 7.55 (m, 1H, ArH), 7.25 (m, 2H, ArH), 7.13 (m, 1H, ArH), 2.54 (s, 3H, CH_3CO), 2.45 (s, 3H, CH_3Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.0 (C-2), 162.5 (C-11), 152.0 (C-15), 144.9 (C-3), 137.8 (C-6), 134.2 (C-12), 131.5 (2C, C-13), 130.8 (C-7), 130.5 (C-5), 130.0 (C-8), 128.9 (C-4), 127.1 (C-10), 126.2 (C-9), 123.8 (2C, C-14), 25.5 (C-1), 20.0 ($ArCH_3$). Anal. Found: C, 66.73; H, 4.87. $C_{18}H_{15}NO_5$. Calc.: C, 66.46; H, 4.65%.

4.2.5. (Z)-4-(α-Naphthyl)-3-(p-nitrobenzoyloxy)-3-buten-2-one (4e)

Using the method A, **1a** was reacted with 0.482 (1.9 mmol) of α-iodonaphthalene (**3e**) at 65°C for 50 h to

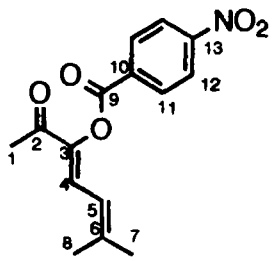


obtain 0.33 g (48%) of **4e**, as a brown reddish solid. M.p. 110–111°C; IR (KBr) 1745, 1680, 1530, 1360, 1260, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.25 (m, 4H, PNB-H), 8.07 (s, 1H, H-4), 8.06 (m, 1H, H-12), 7.89 (dd, J = 7.9, 1.5 Hz, 1H, H-9), 7.87 (br d, J = 8.0 Hz, 1H, H-6), 7.73 (br d, J = 7.3 Hz, 1H, H-8), 7.62 (ddd, J = 1.5, 6.9, 8.1 Hz, 1H, H-11), 7.56 (ddd, J = 1.4, 6.9, 7.9 Hz, 1H, H-10), 7.42 (dd, J = 7.3, 8.0 Hz, 1H, H-7), 2.63 (s, 3H, CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.4 (C-2), 162.8 (C-15), 151.0 (C-19), 145.9 (C-3), 134.0 (C-16), 135.5 (C-13), 131.4 (2C, C-17), 131.3 (C-14), 130.5 (C-6), 128.9 (C-9), 128.1 (C-5), 127.3 (C-8), 127.1 (C-11), 126.8 (C-4), 126.4 (C-10), 125.2 (C-7), 123.7 (C-12 and 2C, C-18), 25.4 (C-1). Anal. Found: C, 69.71; H, 4.20. $C_{21}H_{15}NO_5$. Calc.: C, 69.80; H, 4.18%.

4.3. Preparation of olefins 6a and 6b

4.3.1. (Z)-6-Methyl-3-(p-nitrobenzoyloxy)-3,5-heptadien-2-one (6a)

Under an N_2 atmosphere, 0.2 g (0.85 mmol) of **1a**, 0.115 g (0.85 mmol) of **5a**, 0.006 g (0.026 mmol) of $Pd(OAc)_2$, 4.56 mg (0.015 mmol) of (o-tolyl)$_3$P and 0.212 g (2.1 mmol) of Et_3N were mixed in dry DMF (2 ml) and heated to 120°C for 30 h. The same amounts of **5a**, $Pd(OAc)_2$ and (o-tolyl)$_3$P were added and the mixture was heated to 120°C for 17 h. The mixture was diluted with CH_2Cl_2 (50 ml) and washed with a cold aqueous saturated solution of NH_4Cl (3 × 20 ml). The organic phase was dried ($MgSO_4$) and the solvent was removed in vacuo. The oily residue was purified by flash chromatography with silica gel–10% Et_3N (10 g, hexane–EtOAc, 95:5), giving 0.044 g (18%) of **6a**, as a pale yellow oil. IR (film) 1740, 1680, 1630, 1530, 1350, 1260, 1095, 715 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.26 (s, 4H, ArH), 7.21 (d, J = 11.6 Hz, 1H, H-4), 6.01 (dm, J = 11.6 Hz, 1H, H-5), 2.34 (s, 3H, CH_3CO), 1.89 (br s, 3H, CH_3), 1.83 (br s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.6 (C-2), 162.5 (C-9), 150.8 (C-13), 149.7 (C-6), 142.5 (C-3), 134.2 (C-10), 131.3 (2C, C-11), 126.0 (C-4), 123.5 (2C, C-12), 117.4 (C-5), 26.9 (C-7), 24.9 (C-1), 19.2 (C-8). HRMS m/z calc. for $C_{15}H_{15}NO_5$, 289.0959; found, 289.0952.



4.3.2. (Z)-5-Methyl-3-(p-nitrobenzoyloxy)-3,5-hexadien-2-one (6b)

Under an N_2 atmosphere, 0.2 g (0.85 mmol) of **1a**, 0.103 g (0.85 mmol) of **5b**, 0.006 g (0.026 mmol) of $Pd(OAc)_2$, 4.56 mg (0.015 mmol) of $(o\text{-tolyl})_3P$ and 0.212 g (2.1 mmol) of Et_3N were mixed in dry DMF (2 ml). After heating the mixture to 110°C for 19 h, the same amount of **5b** was added and the heating continued at 110°C for an additional 9 h. Then, the mixture was diluted with CH_2Cl_2 (50 ml) and washed with cold aqueous saturated solution of NH_4Cl (3 × 20 ml). The organic phase was dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was purified by flash chromatography with silica gel–10% Et_3N (10 g, hexane–EtOAc, 95:5), giving 0.075 g (32%) of **6b**, as a pale yellow oil. IR (film) 1745, 1680, 1530, 1350, 1260, 1095, 715 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.32 (m, 4H, PNB-H), 6.96 (s, 1H, H-4), 5.45 (br s, 1H, H-6), 5.36 (m, 1H, H-6), 2.42 (s, 3H, CH_3CO), 2.0 (br s, 3H, CH_3C=); EM (CI, NH_3): 292 ($M^+ + NH_3$, 100), 275 (M^+, 17).

4.4. Preparation of olefins 4a, 6a, 6c and 8a with organotin reagents

4.4.1. General method

In a sealed tube under an atmosphere of air, 0.5 g (1.59 mmol) of **2**, the corresponding trimethyltin reagent (2.08 mmol), and 0.055 g (0.079 mmol) of $(Ph_3P)_2PdCl_2$ in dry $CHCl_3$ (10 ml) was stirred and heated to 100°C for 12 h. The reaction mixture was taken up in CH_2Cl_2 (50 ml), filtered through Celite, washed with deionized water, dried ($MgSO_4$) and the solvent was removed in vacuo. The crude was purified by column chromatography (silica gel, hexane–Et_2O–Et_3N, 5:5:0.1). The solids were recrystallized from ether–hexane.

4.4.2. (Z)-4-Phenyl-3-(p-nitrobenzoyloxy)-3-buten-2-one (4a)

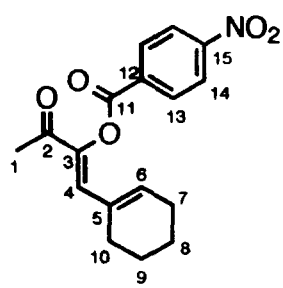
Using the general method, **2** was allowed to react with 0.5 g (2.08 mmol) of Me_3SnPh (**7a**), yielding 0.27 g (55%) of **4a**, as a reddish powder. The physical and spectroscopic properties were identical with those obtained by the Heck method.

4.4.3. (Z)-6-Methyl-3-(p-nitrobenzoyloxy)-3,5-heptadien-2-one (6a)

Using the general method, **2** was allowed to react with 0.45 g (2.08 mmol) of $Me_3Sn(CH{=}CMe_2)$ (**7b**), yielding 0.155 g (34%) of **6a**, as an oil. The physical and spectroscopic properties were identical to those obtained for the same compound prepared by the Heck method.

4.4.4. (Z)-4-(1-Cyclohexenyl)-3-(p-nitrobenzoyloxy)-3-buten-2-one (6c)

Using the general method, **2** was allowed to react with 0.5 g (2.08 mmol) of **7c**, yielding 0.39 g (78%) of **6c**, as a yellow powder. M.p. 159–160°C; IR (nujol) 1748, 1680, 1520, 1380, 1350, 1095 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.31 (s, 4H, ArH), 6.85 (s, 1H, H-4), 6.26 (m, 1H, H-6), 2.35 (s, 3H, CH_3CO), 2.30–2.10 (m, 4H, H-7/H-10), 1.50 (m, 4H, H-8/H-9); ^{13}C NMR (50 MHz, $CDCl_3$): δ 191.7 (C-2), 163.3 (C-11), 151.4 (C-15), 142.0 (C-3), 141.8 (C-6), 134.9 (C-12), 133.5 (C-5), 133.9 (C-4), 131.9 (2C, C-13), 124.2 (2C, C-14), 27.3 (C-7 or C-10), 27.1 (C-10 or C-7), 25.6 (C-1), 22.8 (C-8 or C-9), 21.7 (C-9 or C-8). HRMS m/z calc. for $C_{17}H_{17}NO_5$, 315.1107; found, 315.1105.



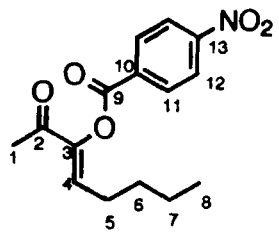
4.4.5. (Z)-3-(p-Nitrobenzoyloxy)-3-penten-2-one (8a)

Using the general method, **2** was allowed to react with 0.37 g (2.08 mmol) of Me_4Sn (**7d**), yielding 0.32 g (81%) of **8a**, as a pale yellow powder. M.p. 104–106°C; IR (nujol) 3000, 1731, 1678, 1272, 1086, 706 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.33 (s, 4H, ArH), 6.72 (q, $J = 7.1$ Hz, 1H, H-4), 2.39 (s, 3H, MeCO), 1.88 (d, $J = 7.1$ Hz, 3H, Me); ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.3 (C-2), 162.3 (C-6), 150.8 (C-10), 147.1 (C-3), 134.2 (C-7), 131.3 (2C, C-8), 129.2 (C-4), 123.6 (2C, C-9), 25.0 (C-1), 12.0 (C-5). Anal. Found: C, 57.70; H, 4.58; N, 5.48. $C_{12}H_{11}NO_5$. Calc.: C, 57.83; H, 4.45; N, 5.62%.

4.5. Preparation of olefin 8b

4.5.1. (Z)-3-(p-Nitrobenzoyloxy)-3-octen-2-one (8b)

The diethyl ether was evaporated from 1.5 ml of a 1.0 M zinc chloride solution. The resulting solid zinc



chloride (1.5 mmol) was then dissolved in 2.5 ml of dry THF under an N_2 atmosphere, cooled to 0°C and 625 μl (1.5 mmol) of 2.5 M of *n*-butyllithium in hexane was added. The resulting *n*-butylzinc chloride (**9**) solution was transferred to a cooled (0°C) solution of 0.314 g (1.0 mmol) of **2** and 0.035 g (0.05 mmol) of $(Ph_3P)_2PdCl_2$ in 2.5 ml of dry THF, using a double-tipped needle under an N_2 atmosphere. The mixture was stirred for 45 min, acidified with saturated aqueous solution of NH_4Cl (50 ml) and extracted into CH_2Cl_2 (3 × 30 ml). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (3 × 20 ml), dried ($MgSO_4$) and the solvent was removed in vacuo. The product was purified by flash chromatography (silica gel, hexane–Et_2O–Et_3N, 8:2:1), yielding 0.116 g (40%) of **8b**, as a yellow oil. IR (nujol) 3000, 1740, 1680, 1520, 1345, 1250, 1090 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.28 (s, 4H, ArH), 6.59 (t, $J = 7.5$ Hz, 1H, H-4), 2.35 (s, 3H, CH_3CO), 2.23 (app. q, $J = 7.0$ Hz, 2H, H-5), 1.45–1.25 (m, 4H, $2CH_2$), 0.86 (t, $J = 7.0$ Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.5 (C-2), 162.4 (C-9), 150.8 (C-13), 146.1 (C-3), 134.2 (C-10), 134.0 (C-4), 131.3 (2C, C-11), 123.6 (2C, C-12), 30.1 (C-5), 26.0 (C-6), 25.0 (C-1), 22.3 (C-7), 13.6 (C-8). HRMS *m/z* calc. for $C_{15}H_{17}NO_5$, 291.1107; found, 291.1100.

4.6. Negishi conditions for the preparation of 4a, 8a and 8b

4.6.1. General method: preparation of (Z)-3-(p-nitrobenzoyloxy)-3-octen-2-one (8b)

To a round-bottomed flask provided with a rubber septum and a magnetic stirrer was added $(Ph_3P)_2PdCl_2$ (0.009 g, 0.0128 mmol) followed by the addition of freshly distilled THF (1 ml) under N_2 atmosphere and the mixture was cooled to 0°C. Then DIBAL-H (0.025 ml, 0.025 mmol) was added and the mixture was stirred for 15 min. To this catalyst mixture was added a THF solution of **2** (0.079 g, 0.25 mmol) and stirred at 0°C for 15 min. In another round-bottomed flask, flushed with N_2, was added freshly fused $ZnCl_2$ (0.051 g, 0.375 mmol) and THF (1 ml). The mixture was cooled to 0°C and *n*-BuLi (0.18 ml, 0.375 mmol) was added and stirred for 15 min. The butylzinc chloride thus prepared was transferred to the Pd–olefin complex prepared above, using a double-tipped needle under N_2 atmosphere. The resulting mixture was stirred for 1.5 h and then quenched with a saturated aqueous solution of NH_4Cl (10 ml). Then it was extracted with CH_2Cl_2 (15 ml). The organic layer was washed successively with water (10 ml), saturated aqueous solution of $NaHCO_3$ (2 × 10 ml) and water (10 ml). The CH_2Cl_2 extract was dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography (silica gel, hexane–EtOAc, 9:1), giving 0.036 g (50%) of **8b**.

4.6.2. (Z)-4-Phenyl-3-(p-nitrobenzoyloxy)-3-buten-2-one (4a)

The general method used for the preparation of **8b** was repeated with phenyllithium (0.225 ml, 0.375 mmol) to obtain 0.042 g (54%) of **4a**.

4.6.3. (Z)-3-(p-nitrobenzoyloxy)-3-penten-2-one (8a)

The general method used for the preparation of **8b** was repeated with methyllithium (0.1 ml, 0.375 mmol) to obtain 0.039 g (62%) of **8a**.

4.7. X-ray crystallography of 8a

Single crystal of **8a** was mounted in a glass capillary. Intensity data were collected on an Enraf–Nonius CAD-4F (kappa geometry) diffractometer with Mo K α radiation (λ = 0.7107 Å; graphite monochromator) at room temperature. The calculations were performed with SHELX 86 [25] and Molen [26]. The unit cell was determined and refined by a least squares method using 25 reflections with $2\theta > 20°$. Final discrepancy indices, R_f and R_{wf} values after least squares refinement are also reported in Table 2. Thermal parameters of all atoms of the structure were refined isotropically. No disorder was present. The positions of all hydrogen atoms were calculated. Intensities were corrected with Lorentz and polarization effects; attenuator and fall-off corrections were also applied. Further details are given in Table 2.

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