

# Preparation of 3-oxo-2-cyclohexen-2-ylzinc iodides and their palladium-mediated reactions with aryl or alkenyl halides

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## Abstract

2-Iodo-2-cyclohexen-1-ones **10** react under mild conditions with a large excess (4 equiv.) of an activated Zn(Ag) couple in the presence of TMEDA (1 equiv.) leading to the corresponding 3-oxo-2-cyclohexen-2-ylzinc iodides **11** in good yields. These new organozinc reagents can also be prepared in high yields by reaction of **10** and TMEDA (1 equiv.) with a large excess (4 equiv.) of 98% pure zinc dust (< 10 micron), which must be activated with chlorotrimethylsilane. In the presence of a palladium(0) catalyst precursor, compounds **11** undergo cross-coupling reactions with aryl or alkenyl halides bearing a variety of functional groups to give in moderate to high yields the desired 2-substituted 2-cyclohexen-1-ones **12**. © 1997 Elsevier Science S.A.

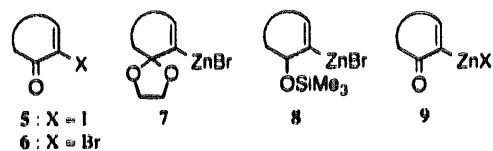
**Keywords:** Zinc; Polyfunctional organozinc derivatives; Palladium catalysis; 2-Substituted 2-cyclohexen-1-ones

## 1. Introduction

2-(1-Alkenyl)- and 2-aryl-2-cycloalken-1-ones of general formula **1** are of considerable importance in organic chemistry. In fact, some 2-(1-alkenyl)-2-cycloalken-1-ones are interesting naturally occurring compounds [1]. Moreover, compounds **1** are useful intermediates for the synthesis of 2-substituted cycloalkanones **2** [2] and could be used for the preparation of 2,3-disubstituted cycloalkanones **3** [3,4] and regiochemically pure 2-substituted cycloalkenyl triflates **4** [5] (Scheme 1).

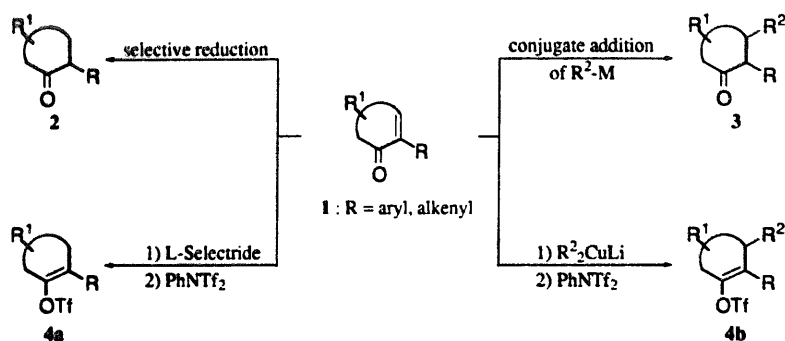
Thus, much attention has been paid to the development of regiospecific procedures for the synthesis of compounds **1** [4,6–9]. Some approaches involve the use of 2-halo-2-cycloalken-1-ones as electrophilic partners of cross-coupling reactions with aryl or alkenyl metals [4,7,8]. In fact, compounds **1** have been efficiently synthesized by palladium- and copper-mediated reaction between 2-iodo-2-cycloalken-1-ones **5** and aryl- or alkenyltributylstannanes [4], by palladium-mediated reaction between (*E*)-1-alkenylboronic acids and 2-bromo-2-cycloalken-1-ones **6** [7] or by palladium-mediated reaction between compounds **5** and arylzinc chlo-

rides [8]. Another regiospecific approach to compounds **1** involves palladium-mediated reactions between aryl or alkenyl halides and the organozinc compounds **7** derived from **6** masked as ketals, followed by acidic hydrolysis of the resulting cross-coupled products [6]. Finally, more recently, it has been developed a new procedure for the synthesis of stereodefined 2-(1-alkenyl)-2-cycloalken-1-ones, which consists of palladium-mediated reactions of 3-trimethylsilyloxy-2-cycloalken-2-ylzinc bromides **8** with stereodefined alkenyl iodides followed by oxidation of the secondary alcohols resulting from removal of the trimethylsilyl group from the cross-coupled products [9].



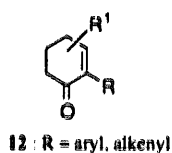
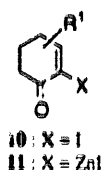
However, protocols involving the direct preparation of compounds **1** from 3-oxo-2-cycloalken-2-ylzinc halides **9** are still unknown. In fact, although procedures for the preparation of several classes of functionalized organozinc derivatives have been well developed [10], the synthesis of compounds **9** has not been reported so far.

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Scheme 1.

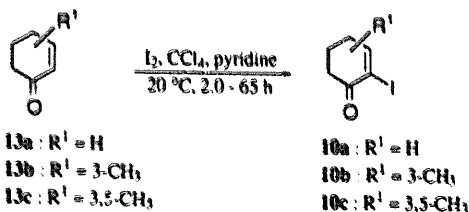
In the context of a program in which we required large amounts of regiochemically pure 2-aryl and 2-(1-alkenyl) substituted cycloalkenyl triflates **4**, we investigated the oxidative addition of zinc to easily available 2-iodo-2-cycloalken-1-ones **5** [11–14] and after some unsuccessful attempts we succeeded in developing two different protocols for the direct preparation of 3-oxo-2-cyclohexen-2-ylzinc iodides of general formula **11** from the corresponding 2-iodo-2-cyclohexen-1-ones **10**.



We now wish to describe these protocols and the use of the organozinc derivatives **11** for the synthesis of 3-aryl and 2-(1-alkenyl) substituted 2-cyclohexen-1-ones of general formula **12**.

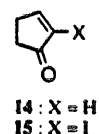
## 2. Results and discussion

Compounds **10a–c**, which were used as starting materials for the synthesis of compounds **11**, were prepared in 45–65% yield by reaction of the corresponding 2-cyclohexen-1-ones **13** with 2 equiv. of iodine dissolved in a 1:1 mixture of pyridine and  $\text{CCl}_4$  at room temperature [11] (Eq. (1)).

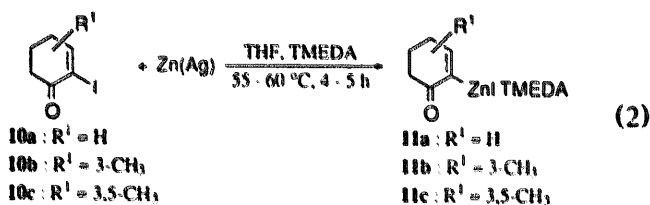


(1)

Similarly, 2-iodo-2-cyclopenten-1-one (**15**) was prepared in 55% yield from 2-cyclopenten-1-one (**14**).



Several attempts were then carried out to convert compounds **10a–c** and **15** into the corresponding organozinc halides. Initially it was attempted to prepare these organometallics by direct reaction of THF solutions of **10a–c** or **15** with zinc dust activated with 1,2-dibromoethane and chlorotrimethylsilane [15]. However, these iodides failed to form the desired products in noticeable amounts and the starting materials could be recovered. Nevertheless, after many trials it was found that a clean formation of compounds **11** could be obtained by addition of THF solutions of compounds **10a–c** and tetramethylethylenediamine (TMEDA) to a THF suspension of a Zn(Ag) couple previously activated with chlorotrimethylsilane (Eq. (2)).



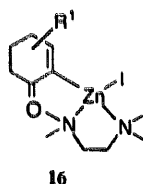
Thus, in a typical preparation of compounds **11**, chlorotrimethylsilane (0.035 equiv.) was added to a suspension of the Zn(Ag) couple (4 equiv.) [16,17] in THF and the mixture was stirred for 20 min at room temperature, for 5 min at 55°C and then cooled to room temperature. A solution of compound **10** (1 equiv.) and TMEDA (1 equiv.) in THF was then added and the

resulting mixture was stirred for 4–5 h at 55–60°C. After this period a GLC/MS analysis of an aliquot of the reaction mixture, which was hydrolyzed with a saturated aqueous  $\text{NH}_4\text{Cl}$  solution, showed the presence of a new compound, which corresponded to the 2-cyclohexen-1-one **13** derived from hydrolysis of the desired organozinc iodide **11**. Interestingly, only small amounts of unreacted **10** (2–3%) were also present. According to this optimized protocol compounds **11a**, **11b** and **11c** were prepared in 95–98% yield.

Alternatively, high yields of compounds **11** were obtained by addition of a THF solution of compounds **10** (1 equiv.) and TMEDA (1 equiv.) to a THF suspension of 98% pure zinc dust (< 10 micron) (4 equiv.) purchased from Aldrich, which was previously activated with chlorotrimethylsilane (0.035 equiv.), and by stirring the reaction mixture at 60°C for 4–5 h. According to this protocol compounds **11a–c** were prepared in yield higher than 95%. However, two aspects of this protocol are worth mentioning. First, the type of zinc dust used in this procedure required careful manipulation since this material is flammable and air- and water-sensitive. Second, settlement of the reaction mixtures, which contained compounds **11** prepared according to this protocol, required periods of time much longer than those which were necessary for settlement of the reaction mixtures derived from the  $\text{Zn}(\text{Ag})$  couple.

Unfortunately, both these protocols proved to be unsuitable for the preparation of the organozinc iodide derived from 2-iodo-2-cyclopenten-1-one (**15**).

As regards the structure of compounds **11**, it must be noted that, although there is no experimental evidence, it seems reasonable to assume that these organometallics have the chelate tetrahedral structure **16**



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In fact, the formation of a tetrahedral complex with  $\text{sp}^3$  hybridization of the zinc atom is expected in view of its  $3\text{d}^{10}4\text{s}^2$  electron configuration [18].

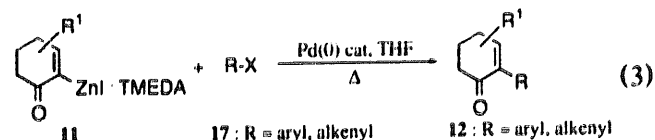
As a part of an effort to explore the synthetic utility of these new organozinc reagents, we next investigated their use in palladium-mediated carbon–carbon bond forming reaction and we found that, in the presence of 5 mol% of a palladium(0) catalyst precursor, compounds **11** reacted with THF solutions of aryl or alkenyl halides, which could contain methoxy, nitro, chloro, fluoro and alkoxy carbonyl groups, to give the corresponding poly-functional cross-coupled products in moderate to excellent yields (Eq. (3)) (Table 1).

Table 1  
Palladium-mediated reactions between the organozinc reagents **11** and aryl or alkenyl halides <sup>a</sup>

Entry	Organozinc reagent <b>11</b>	Organic halide <b>17</b>	Reaction time / temperature (h / °C)	product <b>12</b>	Isolated yield (%) <sup>b</sup>
1	<b>11a</b>		20 / 60		94.6
2	<b>11a</b>		20 / 60		62.6
3	<b>11a</b>		9 / 65		62.0
4	<b>11b</b>		6 / 65		31.7
5	<b>11b</b>		6 / 20 then 6 / 40		15.6 <sup>c</sup>
6	<b>11c</b>		8 / 65		88.9
7	<b>11c</b>		22 / 65		84.2
8	<b>11c</b>		8 / 20 then 23 / 65		70.0
9	<b>11b</b>		23.5 / 65		48.0

<sup>a</sup> The reactions between **11a–c** and compounds **17a–h** (0.74 equiv) were carried out in THF in the presence of 5 mol%  $\text{Pd}(\text{PPh}_3)_4$  (Entries 1–8). The reaction between **11b** and **17i** (0.77 equiv) was carried out in THF in the presence of 5 mol%  $\text{Pd}(\text{dba})_2$  and 15 mol%  $\text{AsPh}_3$  (Entry 9). <sup>b</sup> Based on the amounts of the organic halide used. <sup>c</sup> Compound **12d**, which was obtained in this entry, was contaminated by ca 7% of a stereoisomeric mixture of ethyl 5-ethoxycarbonyl-2,4-pentadienoate (**18**).

Interestingly, preliminary experiments showed that compounds **11**, which were prepared from the  $\text{Zn}(\text{Ag})$  couple, exhibited reactivity similar to those obtained from 98% pure zinc dust. However, since clear THF solution of compounds **11** were easier obtained when these organozinc iodides were prepared from the  $\text{Zn}(\text{Ag})$  couple, the subsequent experiments (Table 1) were performed using compounds prepared according to this protocol.



Thus, the reaction of a THF solution of **11a** with 0.77 equiv. of 2-(methoxy)bromobenzene (**17a**) at 60°C

for 20 h, in the presence of 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, gave 2-(2-methoxyphenyl)-2-cyclohexen-1-one (**12a**) in 94.6% isolated yield (Entry 1, Table 1). Under similar experimental conditions the organozinc iodide **11a** was coupled with  $\alpha$ -bromostyrene (**17b**) and 4-(nitro)bromobenzene (**17c**) to give the desired cross-coupled products, **12b** and **12c**, in 62.6 and 62% isolated yields, respectively (Entries 2 and 3, Table 1). Similar satisfactory results were obtained in the cross-coupling reactions between **11c** and functionalized aryl bromides performed in the presence of 5 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>. In fact, the reactions of **11c** with 4-(chloro)bromobenzene (**17f**), 6-methoxy-2-bromonaphthalene (**17g**) and 3-(fluoro)bromobenzene (**17h**) provided chemoselectively the corresponding 3,5-dimethyl-2-aryl-2-cyclohexen-1-ones, **12e**, **12f** and **12g** in 88.9, 84.2 and 70.0% yields, respectively (Entries 6–8, Table 1). However, modest yields of cross-coupled products were obtained when compounds **11** were reacted with stereodefined 1-halo-1-alkenes in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub>. For example, the crude reaction mixture, which was obtained in the reaction between **11b** and ethyl (*E*)-3-bromopropenoate (**17d**) (Entry 4, Table 1) contained 3-methyl-2-cyclohexen-1-one (**13b**), significant amounts of two stereoisomers of 5-ethoxycarbonyl-2,4-pentadienoate (**18**) and the desired cross-coupled product **12d**.



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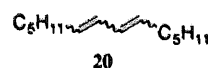


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Compound **13b** derived from hydrolysis of unreacted **11b** and compounds **18** presumably were formed by a transmetalation reaction between **11b** and **17d** followed by a coupling reaction between **17d** and 2-(ethoxycarbonyl)ethenylzinc iodide (**19**) so obtained. Compound **12d** was difficult to isolate from this complex reaction mixture and two consecutive purifications by MPLC on silica gel were necessary to obtain in modest yield (31.7%) this chemically and stereoisomerically pure cross-coupled product. It must be noted that a worse result was obtained in an analogous reaction between **11b** and ethyl (*E*)-3-iodopropenoate (**17e**) (Entry 5, Table 1). In fact, although this reaction was carried out in milder conditions than those used in Entry 4, the crude reaction mixture, which was obtained after hydrolysis, contained larger amounts of **18** and its purification was more difficult than that of the corresponding mixture obtained from **17d**.

Finally, in order to improve the selectivity and yields of the palladium-mediated reactions between compounds **11** and stereodefined 1-halo-1-alkenes, it was thought it right to attempt the use of a catalyst system constituted of Pd(dba)<sub>2</sub> and triphenylarsine. Some re-

cent data showed in fact the beneficial effect of the soft ligand AsPh<sub>3</sub> on the activity of palladium compounds such as PdCl<sub>2</sub>(PhCN)<sub>2</sub>, PdCl<sub>2</sub>(dppf), Pd<sub>2</sub>(dba)<sub>3</sub> or Pd(OAc)<sub>2</sub> in coupling reactions involving organotin [4,19,20], organoboron [21] or organozinc compounds [8,22]. Thus, in a typical experiment, **11b** was reacted with 0.77 equiv. of (*E*)-1-iodo-1-heptene (**17i**) for 23.5 h at 65°C in the presence of 5 mol% Pd(dba)<sub>2</sub> and 15 mol% AsPh<sub>3</sub> (Entry 9, Table 1). GLC/MS analysis of the crude reaction mixture after hydrolysis showed the presence of **13c**, small amounts of three stereoisomers of 6,8-tetradecadiene (**20**) and a compound, which was subsequently identified as stereoisomerically pure **12h**. Purification by MPLC on silica gel allowed to isolate pure **12h** in 48% yield.



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In conclusion, it has been shown that: (i) 2-iodo-2-cyclohexen-1-ones **10** are able to react under mild conditions with an activated Zn(Ag) couple or activated Zn dust, in the presence of TMEDA, to give the corresponding 3-oxo-2-cyclohexen-2-ylzinc iodides **11** in high yields; (ii) these new polyfunctional organozinc reagents undergo cross-coupling reactions with  $\alpha$ -bromostyrene or aryl bromides bearing a variety of functional groups, in the presence of a catalytic amount of Pd(PPh<sub>3</sub>)<sub>4</sub>, to afford the corresponding 2-substituted 2-cyclohexen-1-ones in high yields. On the other hand, modest or low yields of 2-(1-alkenyl)-2-cyclohexen-1-ones have been obtained when compounds **11** were reacted with 1-halo-1-alkenes in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub>. Nevertheless, a model experiment showed that a significant improvement of the yields and selectivity of these reactions can be achieved by using a catalyst system constituted of 5 mol% Pd(dba)<sub>2</sub> and 15 mol% AsPh<sub>3</sub>.

### 3. Experimental

Merck silica gel 60 F<sub>254</sub> precoated aluminum foils were used for thin-layer chromatography (TLC). GLC analyses were performed on a Dani 6500 gas-chromatograph with a PTV injector and equipped with a Dani data station 86.01. Two types of capillary columns were used: a SE-30 bonded FSOT column (30 m × 0.25 mm i.d.) and an AT-WAX bonded FSOT column (30 m × 0.25 mm i.d.). Purifications by MPLC were performed on a Büchi instrument, using a Bischoff 8100 differential refractometer as detector. GLC/MS analyses were performed using a Q-mass 910 spectrometer interfaced with a Perkin-Elmer 8500 gas-chromatograph. <sup>1</sup>H NMR

spectra were recorded on a Varian Gemini 200 MHz spectrometer using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer 1725-X FT-IR spectrophotometer. Melting point (uncorrected) were recorded on a Kofler hot stage apparatus. All air- and water-sensitive reactions were carried out under argon or nitrogen in flame dried glassware. Air- and water-sensitive solutions were transferred with hypodermic syringes or double-ended needles. Solvents were dried, distilled and deaerated before use. The following compounds were prepared according to the literature: Pd(PPh<sub>3</sub>)<sub>4</sub> [23], Pd(dba)<sub>2</sub> [24], ethyl (*E*)-3-bromopropenoate (17d) [25], ethyl (*E*)-3-iodopropenoate (17e) [26], 2-iodo-2-cyclohexen-1-one (10a) [10f]. (*E*)-1-iodo-1-heptene (17i) (b.p. 65–66°C/6 Torr) was prepared from 1-heptyne according to a general procedure reported in the literature [27].

### 3.1. 2-Iodo-3-methyl-2-cyclohexen-1-one (10b)

According to a general procedure reported in the literature [11], a solution of iodine (69.09 g, 272.2 mmol) in a mixture of CCl<sub>4</sub> and pyridine (1:1) (450 ml) was dropwise added under argon to a solution of 3-methyl-2-cyclohexen-1-one (13b) (15.0 g, 136.2 mmol) in a mixture of CCl<sub>4</sub> and pyridine (1:1) (200 ml). The mixture was stirred at room temperature for 24 h, diluted with Et<sub>2</sub>O and washed sequentially with water, 1N HCl, water, 20% aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and water. It was then dried and concentrated in vacuo. The residue was purified by MPLC on silica gel, using a mixture of benzene and Et<sub>2</sub>O (97:3) as eluant, to give chemically pure 10b (20.9 g, 65% yield) as a pale yellow liquid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 2.64–2.52 (4H, m, H-4 and H-6), 2.26 (3H, s, CH<sub>3</sub>), 2.00 (2H, *pseudo* quint, *J* = 6.0 Hz, H-5). MS, *m/z* (relative intensity): 236 (26), 127 (14), 109 (82), 82 (100), 81 (26), 79 (32), 77 (12), 54 (34), 53 (43). Anal. Found: C, 35.76; H, 3.94. C<sub>7</sub>H<sub>9</sub>IO. Calc.: C, 35.62; H, 3.84.

### 3.2. 2-Iodo-3,5-dimethyl-2-cyclohexen-1-one (10c)

According to the procedure reported for the synthesis of 10b, a solution of 3,5-dimethyl-2-cyclohexen-1-one (13c) (10.0 g, 80.53 mmol) in a mixture of CCl<sub>4</sub> and pyridine (1:1) (50 ml) was reacted at room temperature for 65 h with a solution of iodine (40.99 g, 161.06 mmol) in a mixture of CCl<sub>4</sub> and pyridine (1:1) (200 ml). After usual work up, the crude reaction product was purified by MPLC on silica gel, using a mixture of benzene and Et<sub>2</sub>O (98:2) as eluant, to give chemically pure 10c (8.2 g, 41% yield) as a pale yellow solid. M.p. 59–61°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 2.75–2.50 (1H, m, H-5), 2.45–2.10 (7H, br m, H-4, H-6 and CH<sub>3</sub> in the 3-position), 1.07 (3H, d, *J* = 5.4 Hz, CH<sub>3</sub> in the 5-posi-

tion). MS, *m/z* (relative intensity): 251 (5), 250 (58), 208 (57), 81 (24), 79 (11), 77 (11), 53 (100). S<sup>1</sup> (24). Anal. Found: C, 38.37; H, 4.51. C<sub>8</sub>H<sub>11</sub>IO. Calc.: C, 38.42; H, 4.43.

### 3.3. 2-Iodo-2-cyclopenten-1-one (15a)

According to the procedure reported for the synthesis of 10a, a solution of 2-cyclopenten-1-one (14) (25.0 g, 304 mmol) in a mixture of CCl<sub>4</sub> and pyridine (1:1) (50 ml) was reacted for 1 h at room temperature with a solution of iodine (76.91 g, 304 mmol) in a mixture of CCl<sub>4</sub> and pyridine (1:1) (600 ml). After usual work up, the crude reaction product was crystallized from pentane to give chemically pure 15a (34.78 g, 55% yield) as a pale yellow solid. M.p. 70–71°C. (Lit. [11] m.p. 71°C). <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.03 (1H, t, *J* = 2.6 Hz, H-3), 2.81–2.70 (2H, m, H-5), 2.55–2.49 (2H, m, H-4). MS, *m/z* (relative intensity): 209 (4), 208 (76), 152 (6), 127 (19), 81 (9), 53 (100), 51 (22), 50 (18).

### 3.4. Preparation of the Zn(Ag) couple

According to the literature [16,17], 85% chemically pure zinc dust (< 325 mesh) (50 g, 765 mmol) was added to 10% aqueous HCl (350 ml) and the mixture was stirred for 5 min at room temperature. It was then filtered and the solid was washed with dry acetone (3 × 200 ml), Et<sub>2</sub>O (2 × 200 ml) and dried in vacuo. It was then added to a stirred suspension of silver acetate (2.0 g, 12 mmol) in glacial acetic acid (330 ml) which was maintained under reflux. After 1 min the mixture was quickly cooled at 5°C and allowed to settle. The clear supernatant solution was eliminated by siphoning and the solid residue was sequentially washed with glacial acetic acid (170 ml) and Et<sub>2</sub>O (5 × 250 ml) and dried for 20 h at 0.05 Torr. It was then stored under argon at room temperature. It must be noted that the activity of this Zn(Ag) couple remained unchanged over months in the absence of air or moisture.

### 3.5. General procedure for the preparation of 3-oxo-2-cyclohexen-2-ylzinc iodides 11

Chlorotrimethylsilane (0.16 ml, 1.26 mmol) was added to a suspension of the Zn(Ag) couple (3.65 g, 55.98 mmol) in THF (8 ml) and the mixture was stirred for 20 min at room temperature and for 5 min at 55°C. It was then cooled to room temperature and a solution of a 2-iodo-2-cyclohexen-1-one 10 (13.99 mmol) and TMEDA (2.11 ml, 13.99 mmol) in THF (8 ml) was added. The resulting mixture was stirred for 4–5 h at 65°C, cooled to room temperature and allowed to settle. GLC/MS analysis of an aliquot of the clear supernatant solution, which was hydrolyzed with a saturated aque-

ous  $\text{NH}_4\text{Cl}$  solution, showed that it contained the 2-cyclohexen-1-one **13**, derived from hydrolysis of the organozinc iodide **11** so obtained, together with a small amount (2–3%) of unreacted **10**. The clear supernatant THF solution of **11** was then transferred via syringe to a new reaction flask.

Alternatively, compounds **11** were prepared by reacting at 65°C for 4–5 h THF solutions of compounds **10** (13.9 mmol) and TMEDA (13.99 mmol) with a suspension of 98% pure zinc dust (< 10 micron) (3.65 g, 55.98 mmol), which was previously activated with chlorotrimethylsilane (1.26 mmol) according to the above mentioned procedure. The reaction times of this alternative procedure were very similar to those employed when compounds **11** were prepared from the  $\text{Zn}(\text{Ag})$  couple. Nevertheless, the times required to obtain clear THF solutions of compounds **11** were longer than those which were necessary when these organometallics were prepared from the  $\text{Zn}(\text{Ag})$  couple. Therefore, the herewith reported palladium-mediated reactions between compounds **11** and aryl or alkenyl halides were carried out using compounds **11** prepared from the  $\text{Zn}(\text{Ag})$  couple.

### 3.6. General procedure for the palladium-mediated reactions between 3-oxo-2-cyclohexen-2-ylzinc iodides **11** and aryl or alkenyl halides

In a typical experiment a 0.57 M THF solution of a 3-oxo-2-cyclohexen-2-ylzinc iodide **11** (19.2 ml, 10.93 mmol) was added to a solution of an aryl or alkenyl halide **17** (8.41 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (0.48 g, 0.42 mmol) in THF (25 ml), which was prepared immediately prior to use, and the resulting mixture was stirred at the temperature and for the period of time reported in Table 1. The mixture was periodically monitored by GLC/MS analysis of its aliquots, which were hydrolyzed with a saturated aqueous  $\text{NH}_4\text{Cl}$  solution, until compound **17** was consumed. The reaction mixture was then cooled to room temperature, poured into a large excess of a saturated aqueous  $\text{NH}_4\text{Cl}$  solution and extracted repeatedly with  $\text{Et}_2\text{O}$ . The collected organic extracts were washed with water, dried and concentrated under reduced pressure. The residue, which was analyzed by GLC/MS and TLC, was diluted with the solvent which was subsequently used for its purification by MPLC on silica gel, and filtered over Celite. The filtrate was concentrated under reduced pressure and the residue was purified by MPLC on silica gel. Compounds **12a–g** were prepared according to this procedure (Entries 1–8, Table 1).

On the other hand, compound **12h** was prepared from **11b** (11.0 mmol) and (*E*)-1-iodo-1-heptene (**17h**) (1.90 g, 8.47 mmol) using a modification of this procedure in which the catalyst system was constituted of  $\text{Pd}(\text{dba})_2$

(0.24 g, 0.42 mmol) and  $\text{AsPh}_3$  (0.386 g, 1.26 mmol) (Entry 9, Table 1).

### 3.7. 2-(2-Methoxyphenyl)-2-cyclohexen-1-one (**12a**)

The crude reaction product, which was obtained from the reaction between 3-oxo-2-cyclohexen-2-ylzinc iodide (**11a**) and 2-(methoxy)bromobenzene (**17a**) (Entry 1, Table 1), was purified by MPLC on silica gel, using a mixture of benzene and  $\text{Et}_2\text{O}$  (97:3) as eluant, to give in 94.6% yield the title compound as a colourless crystalline solid. M.p. 49–51°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.29 (1H, dt,  $J = 6.3$  and 1.8 Hz, H-3), 7.07–6.88 (4H, m,  $\text{H}_{\text{arom}}$ ), 3.76 (3H, s,  $\text{OCH}_3$ ), 2.59 (2H, t,  $J = 6.7$  Hz, H-6), 2.50 (2H, t,  $J = 5.1$  Hz, H-4), 2.12 (2H, quint,  $J = 6.3$  Hz, H-4). MS,  $m/z$  (relative intensity): 202 (100), 174 (34), 145 (31), 119 (32), 115 (39), 91 (40), 77 (40). IR (KBr): 1674, 1595, 1493, 1353, 1028, 970, 910, 768, 718, 573. Anal. Found: C, 76.97; H, 7.01.  $\text{C}_{13}\text{H}_{14}\text{O}_2$ . Calc.: C, 77.20; H, 6.98.

### 3.8. 2-(1-Phenylethenyl)-2-cyclohexen-1-one (**12b**)

The crude reaction product, which was obtained from the reaction between **11a** and  $\alpha$ -bromostyrene (**17b**) (Entry 2, Table 1), was purified by MPLC on silica gel, using a mixture of benzene and  $\text{Et}_2\text{O}$  (97:3) as eluant, to give in 62.6% yield 99% chemically pure **12b** as an oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.28 (5H, br s,  $\text{C}_6\text{H}_5$ ), 6.95 (1H, t,  $J = 4.2$  Hz, H-3), 5.52 (1H, br d, (*Z*)-H-2'), 5.26 (1H, br d, (*E*)-H-2'), 2.54–2.48 (4H, br m, H-4 and H-6), 2.11 (2H, quint,  $J = 6.3$  Hz, H-5). MS,  $m/z$  (relative intensity): 198 (51), 197 (11), 155 (25), 154 (29), 142 (71), 141 (100), 128 (35), 115 (64), 91 (25). IR (neat): 1680, 1494, 1354, 1165, 977, 907, 907, 779, 701, 606. Anal. Found: C, 84.555; H, 7.33.  $\text{C}_{14}\text{H}_{14}\text{O}$ . Calc.: C, 84.81; H, 7.33.

### 3.9. 2-(4-Nitrophenyl)-2-cyclohexen-1-one (**12c**)

The crude reaction product, which was obtained from the reaction between compound **11a** and 4-(nitro)bromobenzene (**17c**) (Entry 3, Table 1), was purified by MPLC on silica gel, using a mixture of benzene and  $\text{Et}_2\text{O}$  (95:5) as eluant, to give in 62.0% yield chemically pure **12c** as an orange solid. M.p. 75–76°C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.19 (2H, d,  $J = 8.8$  Hz, H-3' and H-5'), 7.49 (2H, d,  $J = 8.8$  Hz, H-2' and H-6'), 7.17 (1H, t,  $J = 4.2$  Hz, H-3), 2.65–2.07 (4H, m, H-4 and H-6), 2.15 (2H, *pseudo* quint,  $J = 6.4$  Hz, H-5). MS,  $m/z$  (relative intensity): 217 (37), 189 (61), 161 (35), 128 (30), 115 (100), 104 (23), 89 (36), 63 (40), 55 (66). IR (KBr): 1677, 1515, 1347, 981, 858, 835, 754, 694. Anal. Found: C, 66.60; H, 5.43.  $\text{C}_{12}\text{H}_{11}\text{NO}_3$ . Calc.: C, 66.35; H, 5.10.

### 3.10. (*E*)-2-[2-(Ethoxycarbonyl)ethenyl]-3-methyl-2-cyclohexen-1-one (**12d**)

GLC/MS analysis of the crude reaction product, which was obtained from the reaction between 1-methyl-3-oxo-2-cyclohexen-2-ylzinc iodide (**11b**) and ethyl (*E*)-3-bromopropenoate (**17d**) (Entry 4, Table 1), showed that it was constituted of five components in a *ca.* 19:15:25:26:15 ratio, which had MS spectra corresponding to 3-methyl-2-cyclohexen-1-one (**13b**), two stereoisomers of ethyl 5-ethoxycarbonyl-2,4-pentadienoate (**18**), the desired cross-coupled product **12d** and triphenylphosphine, respectively. This crude product was purified by MPLC on silica gel, using a mixture of benzene and Et<sub>2</sub>O (90:10) as eluant to give **12d** contaminated by *ca.* 18% of **18**. This product was again purified by MPLC on silica gel using CH<sub>2</sub>Cl<sub>2</sub> and then a mixture of CH<sub>2</sub>Cl<sub>2</sub> and Et<sub>2</sub>O (95:5) as eluant, to give in 31.7% yield 99% chemically pure **12d** as a colourless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.49 (1H, d, *J* = 16.1 Hz, H-1'), 6.61 (1H, d, *J* = 16.1 Hz, H-2'), 4.22 (2H, q, *J* = 7.1 Hz, OCH<sub>2</sub>), 2.54–2.43 (4H, m, H-4 and H-6), 2.14 (3H, s, CH<sub>3</sub>-C=), 2.04–1.92 (2H, m, H-5), 1.30 (3H, t, *J* = 7.1 Hz, CH<sub>3</sub>). MS, *m/z* (relative intensity): 208 (9), 163 (28), 135 (100), 117 (12), 107 (10), 105 (11), 91 (24), 79 (21), 55 (26). IR (neat): 1713, 1676, 1625, 1368, 1287, 1173, 1073, 983, 691. Anal. Found: C, 69.37; H, 7.85. C<sub>12</sub>H<sub>16</sub>O<sub>3</sub>. Calc.: C, 69.21; H, 7.74.

Compound **12d** contaminated by *ca.* 7% of a stereoisomeric mixture of **18** was also obtained in 15.6% yield by purification by MPLC on silica gel of the crude reaction mixture, which was obtained from the palladium-mediated reaction between **11b** and ethyl (*E*)-3-iodopropenoate (**17e**) (Entry 5, Table 1).

### 3.11. 2-(4-Chlorophenyl)-3,5-dimethyl-2-cyclohexen-1-one (**12e**)

The crude reaction product, which was obtained from the reaction between 1,5-dimethyl-3-oxo-2-cyclohexen-2-ylzinc iodide (**11c**) and 4-(chloro)bromobenzene (**17f**) (Entry 6, Table 1), was purified by MPLC on silica gel, using a mixture of CH<sub>2</sub>Cl<sub>2</sub> and hexane (80:20) as eluant, to give in 88.9% yield chemically pure **12e** as a colourless crystalline solid. M.p. 27–28°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.32 (2H, d, *J* = 8.4 Hz, H-3' and H-5'), 6.99 (2H, d, *J* = 8.4 Hz, H-2' and H-6'), 2.63–2.47 (2H, m, H-6), 2.26–2.18 (2H, br m, H-4 and H-5), 1.81 (3H, s, CH<sub>3</sub>-C=), 1.11 (3H, d, *J* = 5.2 Hz, CH<sub>3</sub>-C-). MS, *m/z* (relative intensity): 236 (36), 234 (100), 194 (25), 192 (76), 166 (16), 164 (45), 129 (51), 115 (46), 53 (40). IR (KBr): 1668, 1490, 1377, 1327, 1089, 821, 595. Anal. Found: C, 71.89; H, 6.51. C<sub>14</sub>H<sub>15</sub>ClO. Calc.: C, 71.64; H, 6.44.

### 3.12. 3,5-Dimethyl-2-(6-methoxy-2-naphthyl)-2-cyclohexen-1-one (**12f**)

The crude reaction product, which was obtained from the reaction between **11c** and 6-methoxy-2-bromonaphthalene (**17g**) (Entry 7, Table 1), was purified by MPLC on silica gel, using CH<sub>2</sub>Cl<sub>2</sub> as eluant, to give in 84.2% yield 98% chemically pure **12f** as a colourless crystalline solid, which was recrystallized from methanol. M.p. 120.5–122°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.75–7.65 (2H, m, H<sub>arom</sub>), 7.45 (1H, br s, H<sub>arom</sub>), 7.17–7.07 (3H, m, H<sub>arom</sub>), 3.91 (3H, s, OCH<sub>3</sub>), 2.65–2.45 (2H, m, H-6), 2.35–2.15 (3H, m, H-4 and H-5), 1.83 (3H, s, CH<sub>3</sub>-C=), 1.24 (3H, d, *J* = 5.1 Hz, CH<sub>3</sub>-C-). MS, *m/z* (relative intensity): 281 (21), 280 (100), 238 (7), 210 (27), 195 (14), 165 (12), 153 (7), 152 (17), 89 (4). IR (KBr): 1662, 1622, 1602, 1485, 1379, 1265, 1190, 1027, 852, 818, 479. Anal. Found: C, 81.59; H, 7.31. C<sub>19</sub>H<sub>20</sub>O<sub>2</sub>. Calc.: C, 81.40; H, 7.19.

### 3.13. 3,5-Dimethyl-2-(3-fluorophenyl)-2-cyclohexen-1-one (**12g**)

The crude reaction product, which was obtained from the reaction between **11c** and 3-(fluoro)bromobenzene (**17h**) (Entry 8, Table 1), was purified by MPLC on silica gel, using a mixture of CH<sub>2</sub>Cl<sub>2</sub> and hexane (70:30) as eluant, to give in 70.0% yield chemically pure **12g** as a colourless solid. M.p. 44–46°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.37–7.26 (1H, *pseudo* q, *J* = 7.1 Hz, H-5'), 6.97 (1H, t, *J* = 8.7 Hz, H-6'), 6.84–6.75 (2H, m, H-2' and H-4'), 2.56 (2H, dt, *J* = 6.9 and 5.6 Hz, H-6), 2.26–2.19 (2H, br m, H-4 and H-5), 1.81 (3H, s, CH<sub>3</sub>-C=), 1.11 (3H, d, *J* = 5.4 Hz, CH<sub>3</sub> in the 5-position). MS, *m/z* (relative intensity): 219 (15), 218 (85), 176 (92), 148 (77), 147 (57), 146 (32), 133 (100), 115 (14), 109 (15), 83 (11), 69 (16). IR (KBr): 1663, 1625, 1609, 1378, 1235, 1138, 1060, 918, 896, 879, 786, 700. Anal. Found: C, 77.12; H, 7.01. C<sub>14</sub>H<sub>15</sub>FO. Calc.: C, 77.04; H, 6.93.

### 3.14. (*E*)-2-(1-Heptenyl)-3-methyl-2-cyclohexen-1-one (**12h**)

The crude reaction product, which was obtained from the reaction between **11b** and (*E*)-1-iodo-1-heptene (**17i**) (Entry 9, Table 1), was purified by MPLC on silica gel, using a mixture of CH<sub>2</sub>Cl<sub>2</sub> and hexane (70:30) as eluant, to give in 48% yield stereoisomerically pure **12h** as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 6.07 (1H, d, *J* = 16.0 Hz, H-1'), 5.89 (1H, dt, *J* = 16.0 and 6.4 Hz, H-2'), 2.44–2.38 (4H, m, H-4 and H-6), 2.15 (2H, q, *J* = 6.8 Hz, H-3'), 2.02 (3H, s, CH<sub>3</sub>-C=), 1.97–1.90 (2H, m, H-5), 1.46–1.30 (6H, br m, H-4', H-5' and H-6'), 0.89 (3H, t, *J* = 6.2 Hz, H-7'). MS, *m/z* (relative

intensity): 206 (51), 191 (28), 163 (32), 149 (69), 135 (100), 107 (36), 93 (71), 91 (92), 79 (83). IR (neat): 2857, 1672, 1327, 1123, 973, 934. Anal. Found: C, 81.75; H, 10.91. C<sub>14</sub>H<sub>22</sub>O. Calc.: C, 81.51; H, 10.75.

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